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(54) Vitamin D compounds and method of preparing these compounds

Vitamin-D-Derivate und Verfahren zu deren Herstellung

Dérivés de vitamine D et leur procédé de préparation

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- THE JOURNAL OF ORGANIC CHEMISTRY,
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pages 1264 - 1269 F. J. SARDINA ET AL 'Studies
on the synthesis of side-chain hydroxylated
metabolites of vitamin D. 2. Stereocontrolled
synthesis of 25-hydroxyvitamin D2.'
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Description

The invention relates to new vitamin D compounds, to a method of preparing these compounds and to their use in pharmacology. The invention further relates to valuable new intermediates.

It is generally known, that vitamin D compounds or vitamin D related compounds ("vitamin D compounds") have a strong biological activity and may be used in all those cases in which problems with the calcium metabolism and bone metabolism play a part. A few years ago it was found that various active vitamin D compounds also have other pharmacotherapeutic activities and may be used successfully, for example, for the treatment of certain skin diseases, for cosmetic applications and for treating diseases which are related to cell differentiation, cell proliferation or imbalance in the immune system, including diabetes mellitus, hypertension and inflammatory diseases such as rheumatoid arthritis and asthma. In addition, these compounds may be used in various veterinary applications, and for diagnostic purposes.

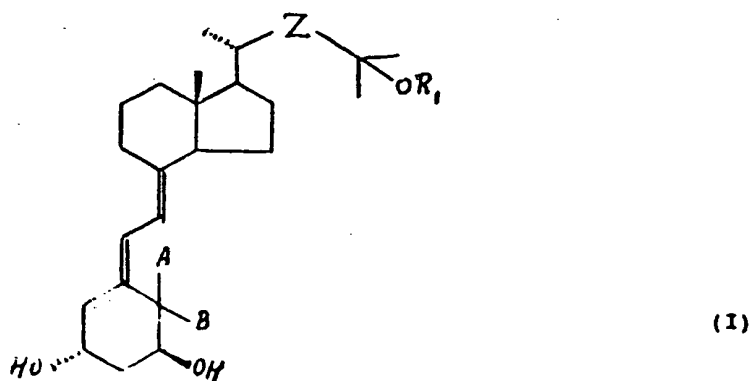
It is therefore of the utmost importance to have the disposal of an arsenal of active vitamin D compounds for the above various application fields so as to be able to make the best possible choice of a vitamin D compound for the application in view.

Vitamin D compounds which are of interest for the above applications are hydroxylated vitamin D compounds, in particular vitamin D compounds hydroxylated in the 1α -, 24- and/or 25-positions. Recent developments in the field of active vitamin D compounds are 19-nor-vitamin D compounds (EP-A-0387077), 25,25-di(cyclo)alkyl vitamin D compounds (non-prepublished US patent application 08/070,998) and (C-18)-modified vitamin D compounds (EP-A-0521550), preferably also hydroxylated in the 1α -position and optionally in the (C-17)-side chain. Other modifications of the (C17)-side chain have been proposed, likewise to improve the intended activity and to suppress detrimental side-effects. Examples of modifications of the (C17)-side chain are chain elongations (homo compounds), 22-oxa modifications, fluor substitutions, epoxy groups (e.g. WO 92/21695), etc. Generally, however, the above (C17)-side chain modified vitamin D compounds are still not completely satisfactory as regards their selective activity, i.e. the intended activity without detrimental side-effects, such as high calcemic and calciuric effects.

It is well-known in the art, that vitamin D₃ metabolizes in the living organism into a number of hydroxylated vitamin D₃ compounds, viz. 25-hydroxy-vitamin D₃ and $1\alpha,25$ -dihydroxy-vitamin D₃. The metabolism of vitamin D₂ is thought to be related to that of vitamin D₃, also resulting in a number of hydroxylated vitamin D₂ metabolites. To investigate these hydroxylated vitamin D₂ metabolites, Sardina et al. (J. Org. Chem., Vol. 51, 1986, 1264-1269) have synthesized 25-hydroxyvitamin D₂, Granja et al. (J. Org. Chem., Vol. 58, 1993, 124-131) have recently synthesized $1\alpha,25$ -dihydroxy-vitamin D₂, and Choudhry et al. (J. Org. Chem., Vol. 58, 1993, 1496-1500) have - also recently - succeeded in the synthesis of $1\alpha,25,28$ -trihydroxy-vitamin D₂. Although during the last decade a great number of publications has been devoted to vitamin D₃ analogues and derivatives as well as to their biological activity, vitamin D₂ compounds have not been explored largely, apparently (also) due to their difficult synthetic accessibility.

It is therefore the objective of the present invention to provide a new class of vitamin D compounds, in particular vitamin D₂ compounds and related compounds, which is well accessible from readily available or accessible starting materials.

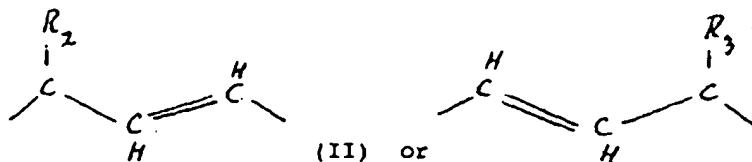
According to the present invention this objective can be achieved with a new vitamin D compound of the general formula



wherein:

R_1 is a hydrogen atom or a hydroxy protecting group;

Z is a group of the general formula



wherein

R_2 and R_3 are each individually straight or branched (C_1 - C_6)alkyl groups or (C_2 - C_6)alkenyl groups, optionally substituted with one or more substituents selected from hydroxy, (C_1 - C_4)alkoxy, fluoro, (C_3 - C_6)cycloalkyl and (C_2 - C_3)alkylenedioxy; or with unsubstituted or substituted phenyl; or (C_3 - C_6)cycloalkyl groups, or unsubstituted or substituted phenyl groups; or wherein R_1 and R_3 together with the interconnecting oxadimethylene biradical form a 5-7 membered ring-closed (C_1 - C_4)alkyl substituted hemiacetal; with the proviso, that R_2 and R_3 are not methyl groups;

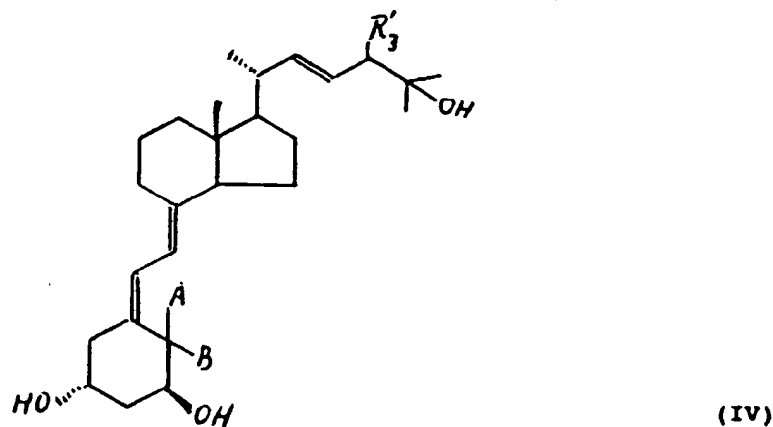
A and B are each individually hydrogen atoms or methyl groups, or A and B form together a methylene group.

The above new vitamin D compounds of the invention, presented by the general formula I, are valuable substances. The biological results indicate that these compounds are promising as biologically active substances and may be used in all above-mentioned pharmacotherapeutic indications, more in particular for the treatment of osteoporosis, renal osteodystrophy, osteomalacia, skin disorders such as psoriasis (and other hyperproliferative skin diseases), eczema and dermatitis, myopathy, leukemia, breast and colon cancer, osteosarcomas, squamous cell carcinomas, melanoma, certain immunological disorders, and transplant rejections.

Furthermore, the new vitamin D compounds of the invention may be used for wound healing and may be incorporated in cosmetic compositions, such as creams, lotions, ointments and the like, in order to preserve, condition and/or protect the skin and to improve various skin conditions, such as wrinkles, dry skin, skin slackness and insufficient sebum secretion. The new vitamin D compounds may also be used for diagnostic purposes.

Suitable substituents of the above phenyl group are: (C_1 - C_4)alkyl, (C_1 - C_4)alkoxy, fluoro, trifluoromethyl and hydroxy.

Preferred is a vitamin D compound of the general formula



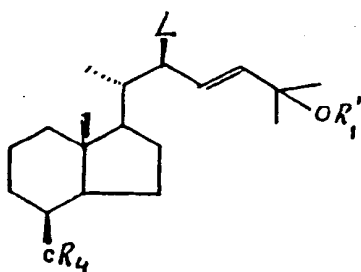
wherein:

A and B have the meanings given above, and

R_3' is a straight or branched (C_2-C_6)alkyl group, optionally substituted with hydroxy, (C_1-C_2)alkoxy or (C_2-C_3)alkylenedioxy, a cyclopropyl group or a phenyl group.

It is a merit of the present invention, that the desired C-24 stereo-isomer can easily be obtained, as will be explained hereinafter. Therefore the present invention also relates to a vitamin D compound of the above general formula IV, wherein the C-24 atom, i.e. the carbon atom to which R_1' is attached, has either the *R* or the *S* configuration.

The invention also relates to a method of preparing a vitamin D compound of the above formula I as defined above, in that a hydrindane compound of the general formula

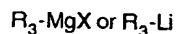


(V)

wherein:

L is a suitable leaving group, and

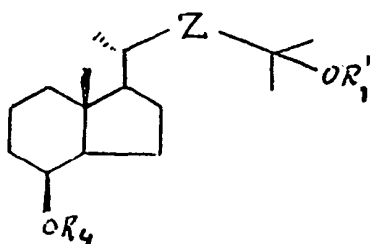
R_1' and R_4 are each individually hydroxy-protecting groups; is reacted with a reagent of the general formula



wherein

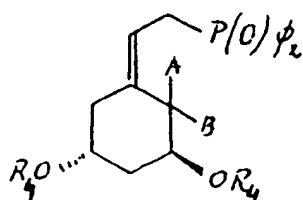
R_3 has the meaning given hereinbefore, and
 X is a halogen atom,

in the presence of a $Cu(I)$ compound;
 after which the hydrindane intermediate obtained, having the general formula



(VI)

wherein Z has the meaning given above,
 is oxidized, after deprotection of OR_4 , to the corresponding hydrindane-4-one compound, and is then converted, in a manner known per se for related compounds,
 either (a) with a Wittig reagent of the general formula

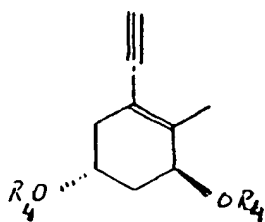


(VII)

wherein:

R_4 has the above meaning, and
A and B have the meanings given hereinbefore,

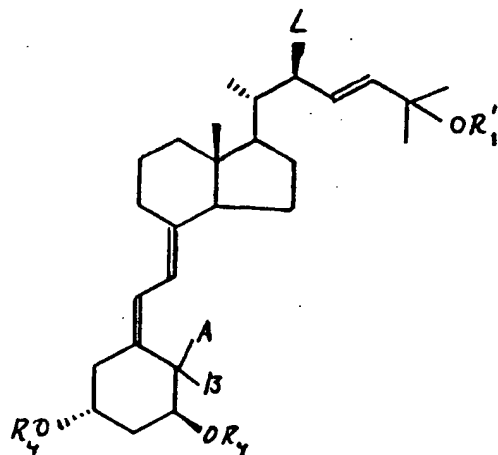
or (b), after enolization, with an enyne compound of the general formula



(VIII)

wherein R_4 has also the above meaning, followed by hydrogenation and isomerization, to produce a compound of the general formula I, wherein A and B form together a methylene group; followed by deprotection.

Alternatively, the vitamin compound of the above formula I as defined above can be prepared with a method wherein a hydrindane compound of the general formula V as defined above is oxidized, after deprotection of OR_4 , to the corresponding hydrindane-4-one compound, and is then converted, in a manner known per se for related compounds, either (a) with a Wittig reagent of the general formula VII as defined above to produce a compound of the general formula



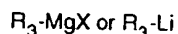
(XII)

wherein:

L is a suitable leaving group;
 R_1' and R_4 are each individually hydroxy protecting groups; and
A and B are each individually hydrogen atoms or methyl groups,

or A and B form together a methylene group

or (b) after enolization with an enyne compound of the general formula VIII as defined above, followed by hydrogenation and isomerization, to produce a compound of the general formula XII, wherein A and B form together a methylene group; followed by reaction with a reagent of the general formula



wherein:

R_3 has the meaning given hereinbefore, and
X is a halogen atom,

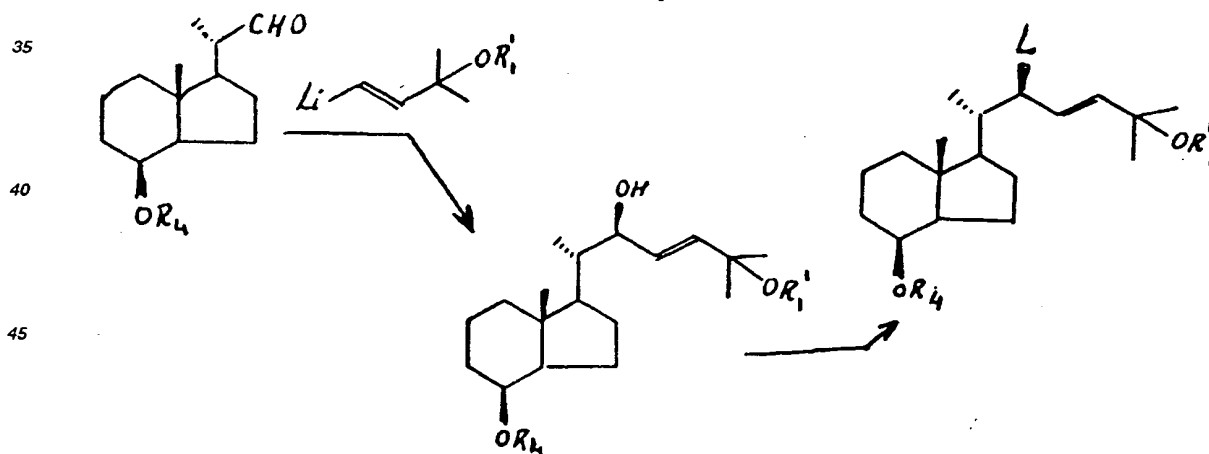
in the presence of a Cu(I) compound;
followed by deprotection.

Examples of suitable leaving groups L are: phosphate esters, sulphonates such as tosylate and mesylate, and N-arylcarbamates.

Hydroxy groups in the above intermediates or reactants may be protected by a reaction with a suitable etherification agent; for example, a methoxymethylating agent (such as methoxymethylchloride), a trialkylsilylimidazole, a trialkylsilylhalide, a trialkyl-silyltriflate (-trifluoromethanesulfonate), a diphenylalkylsilylhalide, or a diphenylalkylsilyltriflate, or a derivative thereof, the alkyl groups of which have 1 to 6 carbon atoms. Particularly suitable for this purpose are trimethylsilylchloride, tert.-butyldimethylsilylchloride, dimethyl-(1,1,2-trimethylpropyl)-silylchloride, tert.-butyldimethylsilyl triflate, or trimethylsilyl-imidazole, because these etherification agents readily react with the hydroxy group to be protected to form an ether function, which on the one hand is sufficiently stable under the conditions of the reaction or reactions in view, but on the other hand can easily be removed [deprotection] to recover the original hydroxy group; tert.-butyldimethylsilylchloride or triflate is to be preferred, because the tert.-butyldimethylsilyl group has been found to be excellently suitable as a protective group.

The enolic hydroxy group is preferably derivatized by a reaction with N-phenyltriflimide to produce a triflate.

The starting compounds of formula V can conveniently be prepared from readily available substances, e.g. as follows:



The second reaction step, i.e. the conversion of the hydroxy group in the intermediate allylic hydroxy compound to a leaving group L can be performed with the aid of various compounds, viz.:

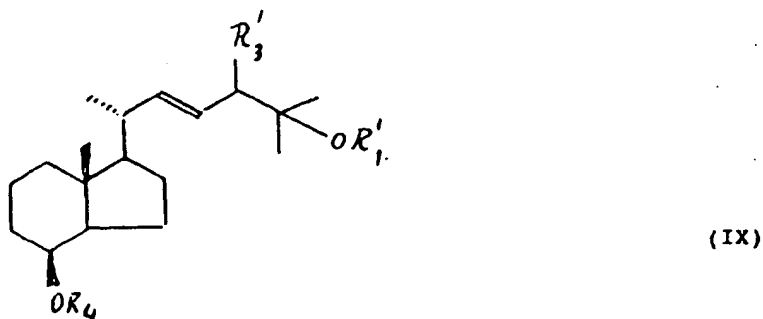
- sulphonating compounds, such as tosylchloride and mesylchloride;
- phosphate-introducing compounds, such as $ClPO(O\text{-hydrocarbyl})_2$; and
- N-arylcarbamoyl-introducing compounds, such as phenylisocyanate.

The term hydrocarbyl includes: (C_1-C_4) alkyl, phenyl, phenyl (C_1-C_2) alkyl and cyclohexyl.

In this manner formula V compounds are prepared, wherein L is a hydrocarbyl sulphonate, a dihydrocarbyl phosphate or a N-arylcarbamate group, respectively.

The hydrindane intermediate of the above general formula VI is new. Therefore the present invention also relates to this intermediate, as well as to a method of preparing this compound.

A preferred hydrindane intermediate as defined above can be represented by the general formula

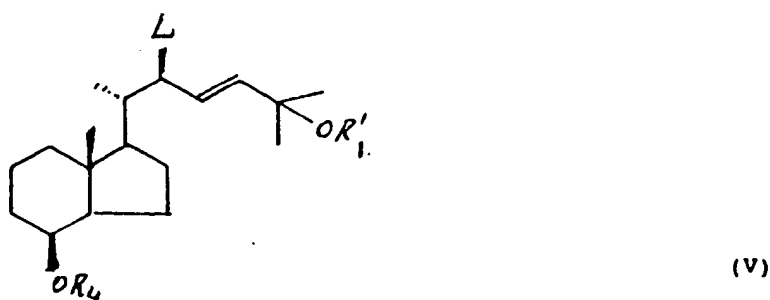


wherein:

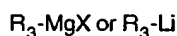
R_1' , R_3' and R_4 have the meanings given above.

Substantially pure C-24 enantiomeric vitamin D compounds can be obtained by using substantially pure hydrindane stereoisomers as intermediates. The present invention therefore also relates to a hydrindane intermediate of the above general formula IX, wherein the C-atom, to which substituent R_1' is attached, has either the *R* or the *S* configuration. As will be explained hereinafter, these isomers can be prepared stereospecifically in a convenient manner.

The hydrindane compound of the general formula VI, defined above, can be prepared conveniently by reacting a hydrindane compound of the general formula



wherein L, R_1' and R_4 have the meanings given above, with a reagent of the general formula



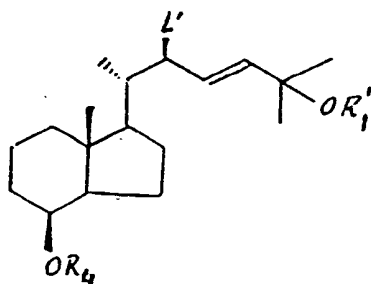
wherein R_3 has the meaning given above and X is a halogen atom, in the presence of a Cu(I) compound.

Examples of suitable reagents for the above reaction are:

$R_3\text{-MgBr}$, $R_3\text{-MgI}$, $R_3\text{-MgCl}$ and $R_3\text{-Li}$, wherein R_3 is defined above; examples of suitable cupro compounds are CuCN, CuCl and CuI.

It has been found, that the above-mentioned hydrindane stereoisomers of the general formula IX, wherein the C-atom, to which substituent R_3' is attached, has either the *R* or the *S* configuration, can be prepared selectively by using as the starting substance a hydrindane compound of the general formula V having a specific leaving group L.

So a hydrindane intermediate of formula IX, wherein said C-atom has the configuration as shown in formula IXA below, can be prepared selectively from a hydrindane compound of the general formula

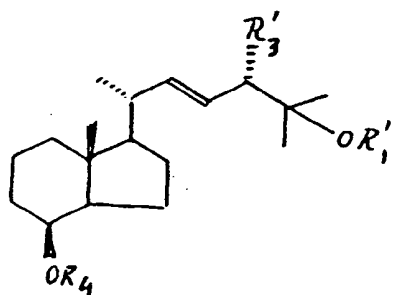


(X)

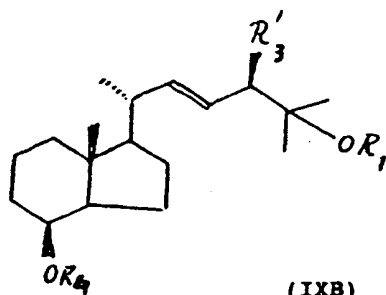
wherein:

R_1' and R_4 have the meanings above, and
 L' is a di(hydrocarbyl)phosphate leaving group.

If, however, a hydrindane intermediate of formula IX is desired, wherein said C-atom has the configuration as shown in formula IXB below, as the starting substance a hydrindane compound can excellently be used, wherein L' is a N-arylcarbamate leaving group.



(IXA)



(IXB)

To improve the applicability of the new vitamin D compounds of the invention for the above-described pharmacotherapeutic indications, the compounds are usually processed to pharmaceutical compositions, comprising an effective amount of said vitamin D compound as the active ingredient in addition to a pharmaceutically acceptable carrier and/or at least one pharmaceutically acceptable auxiliary substance. Such a composition may be delivered in a dosage unit form for oral, topical (dermal) or parenteral administration, comprising approx. 0.1 μ g to approx. 0.1 mg active ingredient per dosage unit.

A composition for diagnostic purposes may comprise, in addition to the vitamin D compound of the present invention, a compatible, non-toxic carrier and/or at least one auxiliary substance.

A cosmeceutical composition may comprise, in addition to an effective amount (in the range of approx. 0.1 μ g to approx. 0.1 mg per dosage unit in a dosage unit form) of the vitamin D compound of the present invention, a cosmetically acceptable, non-toxic carrier and/or at least one auxiliary substance.

Finally the invention relates to a composition when for use in a method for the treatment and prophylaxis of a number of disease states including autoimmune diseases (including diabetes mellitus), acne, alopecia, skin aging (including photo-aging), imbalance in the immune system, inflammatory diseases such as rheumatoid arthritis and asthma, as well as diseases related to abnormal cell differentiation and/or proliferation, in a warm-blooded living being, comprising administering to said being or treating said being with a pharmaceutical composition as defined above in a quantity effective for the intended purpose. Examples of such diseases are psoriasis and other hyperproliferative skin diseases.

The present invention also relates to the use of the above pharmaceutical compositions for the treatment of solid, skin and blood cancers, in particular of blood cancers such as leukemia, of breast cancer, and of skin cancers such as

melanoma and squamous cell carcinoma.

The above-defined cosmeceutical compositions, in particular selected from the group consisting of creams, lotions, ointments, liposomes and gels, can be used for the treatment and prevention of a number of skin disorders, such as inadequate skin firmness or texture, insufficient skin hydration, wrinkles and insufficient sebum secretion.

The invention will now be described in greater detail with reference to the following specific Examples.

The following abbreviations are used in the examples:

THF = tetrahydrofuran

TBS = tert.-butyl dimethyl silyl

MOM = methoxymethyl

TBAF = tert.-butyl ammonium fluoride

PPTS = pyridinium p-toluene sulphonate

PDC = pyridinium dichromate

AIBN = azodiisobutyronitrile

DCM = dichloromethane

Examples

Example I

Preparation of hydrindane compounds, intermediates for modified vitamin D₂ compounds.

The reaction equations are presented in the Reaction Scheme A appended.

(a). Preparation of compound 2.

Compound 1 is prepared as described by Sardina et al. in J. Org. Chem. 1986, 51, 1264. A mixture of compound 1 (0.50 g, 3.90 mmol), n-Bu₃SnH (1.4 ml, 1.51 g, 5.20 mmol) and AIBN (20 mg) is irradiated with a tungsten lamp of 300 W for 15 min. and then heated at 95°C for 6 h. The reaction mixture is allowed to reach room temperature and is then chromatographed (silica gel; eluent: 0-7% EtOAc/hexane), producing compound 2 in a yield of 1.36 g, 83%, Rf=0.4 (10% EtOAc/hexane), liquid, b.p. 120°C/1 mm Hg.

¹H-NMR: 6.02 (2H, AB, J=19.5 Hz, HC=CH), 4.63 (2H, s, OCH₂O), 3.35 (3H, s, OCH₃), 1.47 (6H, m, Sn(CH₂)₃), 1.30 (6H, s, 2CH₃), 1.29 (6H, m, Sn(CH₂CH₂)₃), 0.91-0.85 (15H, m, (-CH₂CH₃)₃).

¹³C-NMR: 153.26 (C=), 126.58 (C=), 91.97 (OCH₂O), 77.76 (COMOM), 54.98 (OCH₃), 29.01 (SnCH₂)₃, 27.12 (Sn(CH₂CH₂)₃), 26.75 ((CH₃)₂), 13.55 ((-CH₃)₃), 9.42 ((-CH₂CH₃)₃).

(b). Preparation of compound 6.

Compound 5 is prepared from compound 4 as described by Mascarenas et al. in J. Org. Chem. 1986, 51, 1269. Compound 6 is prepared from compound 5 as described by Fernandez et al. in J. Org. Chem. 1992, 57, 3173.

(c). Preparation of compound 7.

A solution of n-BuLi in hexane (2.38 M, 3 ml, 7.11 mmol) is added dropwise to a solution of compound 2 (2.98 g, 7.11 mmol, freshly distilled) in 19 ml Et₂O, cooled at -80°C. The mixture is stirred for 4 hours and then cooled to -85°C. During the reaction compound 3 is intermediately formed in situ. Thereupon a solution of compound 6 (1.49 g, 4.59 mmol) in 36 ml Et₂O, cooled at -85°C, is added in 15 minutes. After stirring for 2 h, a drop of MeOH is added. The reaction is allowed to reach room temperature, after which a saturated NaCl solution (50 ml) and HCl (10%, 2 ml) are added. Extraction with Et₂O (2x30 ml), drying, filtration and concentration yields a residue which is chromatographed over a silica gel column; eluent: 10% EtOAc/hexane. Products 7 [1.58 mg, 76%, Rf=0.61 (30% EtOAc/hexane); crystallizing upon cooling, m.p. 49°C] and 7a [0.24 mg, 11%, Rf=0.57 (30% EtOAc/hexane)] are obtained. Compound 7 is identified by ¹H-NMR and ¹³C-NMR.

¹H-NMR: 5.66 (1H, d, J=16.1 Hz, H-24), 5.58 (1H, dd, J=16.1 and 3.5 Hz, H-23), 4.62 (2H, s, OCH₂O), 4.25 (1H, s, H-22), 3.98 (1H, s, H-8), 3.33 (3H, s, OCH₃), 1.31 (6H, s, CH₃-26 and 27), 0.90 (3H, s, CH₃-18), 0.86 (9H, s, SiC(CH₃)₃), 0.82 (3H, d, J=5.93 Hz, CH₃-21), -0.01 (3H, s, SiCH₃), -0.03 (3H, s, SiCH₃).

¹³C-NMR: 135.00 (C=), 132.58 (C=), 91.75 (OCH₂O), 75.88 (C-25), 73.35, 69.41, 54.95 (OCH₃), 53.13, 52.98, 41.95 (C-13), 40.81, 40.60 (CH₂), 34.35 (CH₂), 27.32 and 27.24 (C-26 and C-27), 26.81 (CH₂), 25.74 (SiC(CH₃)₃), 22.93 (CH₂), 17.94 (SiC(CH₃)₃), 17.58 (CH₂), 13.57, 11.78, -4.89 (SiCH₃).

(d). Preparation of compound 8.

A solution of n-BuLi in hexane (2.38 M, 1.26 ml, 3.0 mmol) is added to a solution of compound 7 (1.24 g, 2.71

mmol) in 25 ml Et₂O while stirring and cooling at -78°C. After 15 min, ClPO(OEt)₂ (0.43 ml, 0.52 g, 3.0 mmol, distilled over P₂O₅) is added. The mixture is stirred for 3 h, and then poured onto a mixture of saturated aqueous NaCl (100 ml) and ice (50 ml). The mixture is extracted with Et₂O (3x40 ml); the organic layer is dried, filtered, concentrated and chromatographed over a silica gel column (eluent: 15-30% EtOAc/hexane), to produce compound 8 in a yield of 1.50 g [93%, Rf=0.3 (30% EtOAc/hexane)].

¹H-NMR: 5.71 (1H, d, J=15.95 Hz, H-24), 5.60 (1H, dd, J=15.95 and 5.0 Hz, H-23), 4.89 (1H, t, J=6.0 Hz, H-22), 4.64 (2H, s, OCH₂O), 4.14-3.97 (4H, m, J=7.2 Hz, P(OCH₂CH₃)₂), 3.97 (1H, s, H-8), 3.34 (3H, s, OCH₃), 1.35-1.26 (6H, m, P(OCH₂CH₃)₂), 1.32 (6H, s, CH₃-26 and 27), 0.91 (3H, d, J=6.33 Hz, CH₃-21), 0.90 (3H, s, CH₃-18), 0.87 (9H, s, SiC(CH₃)₃), -0.01 (3H, s, SiCH₃), -0.02 (3H, s, SiCH₃).

¹³C-NMR: 137.50, 128.04, 91.74 (OCH₂O), 81.16 (d, J=6.9 Hz, C-22), 75.50 (C-25), 69.23, 63.23 (c, J=2.8, P(OCH₂CH₃)₂), 54.85 (OCH₃), 52.92, 52.53, 41.91 (C-13), 41.83, 40.49 (CH₂), 34.18 (CH₂), 27.06 (C-26 and 27), 26.75 (CH₂), 25.59 (SiC(CH₃)₃), 22.84 (CH₂), 17.79 (SiC(CH₃)₃), 17.41 (CH₂), 15.95 (c, J=3.5 Hz, P(OCH₂CH₃)₂), 13.32, 12.16, -5.04 (SiCH₃), -5.40 (SiCH₃).

Example II

Preparation of compound 25 from compound 8.

The reaction equations are presented in the Reaction Scheme B appended.

(a). Preparation of compound 9.

A mixture of CuCN (0.90 g, 10 mmol) and LiCl (0.85 g, 20 mmol) in 28 ml THF is stirred at room temp. until a homogeneous solution is obtained. After cooling to -78°C, a solution of n-BuMgCl in Et₂O (2M, 5 ml, 10 mmol) is added. The resulting reaction mixture is stirred for 5 min. A solution of phosphate 8 (0.96 g, 1.62 mmol, dried over P₂O₅) in 32 ml THF is added. The reaction mixture is stirred for 10 h, after which the mixture is allowed to reach room temperature without removing the cooling bath (12 h). After dropwise addition of a saturated solution of NH₄Cl (30 ml), the mixture is stirred for 10 min and then extracted with hexane (3x50 ml). The organic phase is dried, filtered and concentrated, yielding 784 mg of compound 9 [98%, Rf=0.8 (10% EtOAc/hexane)].

¹H-NMR: 5.20 (1H, dd, J=15.2 and 8.5 Hz, H-22 or H-23), 5.03 (1H, dd, J=15.2 and 9.2 Hz, H-22 or H-23), 4.69 (2H, s, OCH₂O), 3.98 (1H, s, H-8), 3.36 (3H, s, OCH₃), 1.16 (3H, s, CH₃-26 or 27), 1.11 (3H, s, CH₃-26 or 27), 0.98 (3H, d, J=6.59 Hz, CH₃-21), 0.92 (3H, s, CH₃-18), 0.88 (12H, s and t, SiC(CH₃)₃ and (CH₂)₃CH₃), 0.00 (3H, s, SiCH₃), -0.01 (3H, s, SiCH₃).

¹³C-NMR: 139.75 (C=), 128.14 (C=), 90.91 (OCH₂O), 78.31 (C-25), 69.51, 56.56, 55.08, 53.17, 42.03 (C-13), 40.67 (CH₂), 39.98, 34.45 (CH₂), 30.17 (CH₂), 28.26 (CH₂), 27.86 (CH₂), 25.76 (SiC(CH₃)₃), 25.52, 23.12 (CH₂), 23.06, 22.65 (CH₂), 20.69, 17.98 (SiC(CH₃)₃), 17.64 (CH₂), 14.07, 13.88, -4.87 (SiCH₃), -5.24 (SiCH₃).

(b). Preparation of compound 13.

Compound 9 is added to a solution of TBAF in THF (1.1 M, 6 ml, 6.6 mmol). The reaction mixture is stirred for 24 h at 70°C and 48 h at room temperature. The reaction mixture is then poured into a saturated aqueous solution of NaHCO₃ (100 ml) and extracted with Et₂O (3x30 ml). The combined ether layers are dried, filtered and concentrated. The residue is chromatographed over silica gel (eluent: 9% EtOAc/hexane), yielding 471 mg of compound 13 [80%, Rf=0.4 (15% EtOAc/hexane)].

¹H-NMR: 5.18 (1H, dd, J=15.18 and 8.39 Hz, H-22 or H-23), 5.03 (1H, dd, J=15.18 and 9.10 Hz, H-23 or H-22), 4.67 (2H, s, OCH₂O), 4.04 (1H, s, H-8), 3.33 (3H, s, OCH₃), 1.14 (3H, s, CH₃-26 or 27), 1.09 (3H, s, CH₃-26 or 27), 0.97 (3H, d, J=6.61 Hz, CH₃-21), 0.92 (3H, s, CH₃-18), 0.84 (3H, t, J=6.92 Hz, (CH₂)₃CH₃).

¹³C-NMR: 139.46 (C=), 128.32 (C=), 90.87 (OCH₂O), 78.26 (C-25), 69.35, 56.38, 55.07, 53.12, 52.69, 41.71 (C-13), 40.30 (CH₂), 39.92, 33.57 (CH₂), 30.15 (CH₂), 28.19 (CH₂), 27.70 (CH₂), 25.49, 23.06, 22.61 (CH₂), 22.53 (CH₂), 20.61, 17.38 (CH₂), 14.05, 13.64.

(c). Preparation of compound 17.

To a solution of 196 mg (0.517 mmol) of compound 13 in 6 ml DCM are added 0.58 g (1.55 mmol) PDC and approx. 5-10 mg PPTS. After stirring at room temp. for 3.5 h, 20 ml Et₂O is added. Separation of the organic phase, filtration over silica gel and evaporation yields 0.18 g of a residue, which after flash chromatography (silica gel; eluent: EtOAc/hexane 1:20) gives the desired product 17 in a yield of 175.5 mg (90%).

(d). Preparation of protected vitamin D compound 21.

To a solution of the phosphine-oxide 45 (370 mg, 0.63 mmol) in 5 ml dry THF at -78°C is added a small amount of n-BuLi in THF (2.5 M, approx. 230 μl) until the reaction mixture colours red. Thereupon n-BuLi in THF (2.5 M,

254 μ l, 0.63 mmol) is added dropwise. After stirring for 5 min, a solution of 80.1 mg (0.21 mmol) of compound 17 in 2 ml dry THF is added. The mixture is stirred for 0.5 h and allowed to reach room temperature. Purification by flash- chromatography yields 53.4 mg (34%) of the desired title compound 21.

(e). Preparation of vitamin D compound 25.

Compound 21 is dissolved in a 0.83 M solution of TBAF (2.3 ml, 1.88 mmol, 20 eq.) in THF. The mixture is stirred overnight at ambient temperature. The solvent is evaporated and the residue is taken up with Et₂O and washed with brine. The organic phase is dried over MgSO₄ and the solvent evaporated. The residue is quickly chromatographed over silica (Et₂O) and the resulting product is dissolved in methanol (7 ml) and 1.15 g of Dowex^R resin (acidic resin) AG 50W-X4 (washed with MeOH (4x10 ml)) is added. After stirring overnight, filtration and washing with EtOAc (3x20 ml), the reaction mixture is evaporated. The desired vitamin D compound 25 is obtained in a yield of 20 mg as a white solid.

Example III

Preparation of compound 26 from compound 8.

The reaction equations are presented in the Reaction Scheme B appended. Via a reaction sequence analogous to that described in Example II, Vitamin D compound 26 is prepared from compound 8, via the intermediate compounds 10, 14, 18 and 22.

Compound 10 is identified by ¹H-NMR and ¹³C-NMR:

¹H-NMR: 5.25 (1H, dd, J=15.2 and 8.1 Hz, H-22 or H-23), 5.14 (1H, dd, J=15.2 and 7.9 Hz, H-23 or H-22), 4.73 (2H, s, OCH₂O), 3.99 (1H, s, H-8), 3.37 (3H, s, OCH₃), 1.25 (3H, s, CH₃-26 or 27), 1.24 (3H, s, CH₃-26 or 27), 0.98 (3H, d, J=6.58 Hz, CH₃-21), 0.92 (3H, s, CH₃-18), 0.88 (9H, s, Si(CH₃)₃), 0.92-(-0.04) (5H, 5m, c-Pr), 0.00 (3H, s, SiCH₃), -0.01 (3H, s, SiCH₃).

¹³C-NMR: 138.95 (C=), 126.64 (C=), 90.93 (OCH₂O), 78.86 (C-25), 69.94, 56.75, 56.48, 54.93, 53.19, 41.99 (C-13), 40.68 (CH₂), 40.00, 34.44 (CH₂), 27.85 (CH₂), 25.76 (Si(CH₃)₃), 24.88 (C-26 or C-27), 24.73 (C-26 or C-27), 23.14 (CH₂), 20.69, 17.94 (Si(CH₃)₃), 17.64 (CH₂), 13.90, 11.14, 5.49 (CH₂(c-Pr)), 2.41 (CH₂(c-Pr)), -4.89 (SiCH₃), -5.26 (SiCH₃).

Compound 14 is identified by ¹H-NMR and ¹³C-NMR:

¹H-NMR: 5.27 (1H, dd, J=15.22 and 8.42 Hz, H-22 or H-23), 5.14 (1H, dd, J=15.22 and 8.18 Hz, H-23 or H-22), 4.72 (2H, s, OCH₂O), 4.06 (1H, s, H-8), 3.36 (3H, s, OCH₃), 1.24 (6H, s, CH₃-26 and 27), 0.98 (3H, d, J=6.60 Hz, CH₃-21), 0.93 (3H, s, CH₃-18), 0.92-(-0.06) (5H, 5m, c-Pr).

¹³C-NMR: 138.61 (C=), 126.79 (C=), 90.84 (OCH₂O), 74.84 (C-25), 69.20, 56.68, 56.26, 54.92, 52.67, 41.65 (C-13), 40.26 (CH₂), 39.87, 33.52 (CH₂), 27.58 (CH₂), 24.79 and 24.71 (C-26 and C-27), 22.50 (CH₂), 20.59, 17.34 (CH₂), 13.59, 11.09, 5.52 and 2.39 (CH₂CH₂(c-Pr)).

Compound 26 is identified by ¹H-NMR and ¹³C-NMR:

¹H-NMR (δ , CD₂Cl₂): 6.23 (1H, d, J=11.2 Hz), 6.00 (1H, d, J=11.2 Hz), 5.30-5.27 (2H, m), 5.26 (1H, s), 4.94 (1H, s), 4.36 (1H, dd, J=4.4 and 6.5 Hz), 4.15 (1H, m), 2.82 (1H, d, J=12.5 Hz), 2.53 (1H, dd, J=2.66 and 13.3 Hz), 2.25 (1H, dd, J=6.5 and 13.3 Hz), 1.19 (3H, s), 1.16 (3H, s), 1.02 (3H, d, J=6.6 Hz), 0.73 (1H, m), 0.55 (3H, s), 0.53 (1H, m), 0.36 (1H, m), 0.22 (1H, m), 0.02 (1H, m).

¹³C-NMR (δ , CD₂Cl₂): 148.41, 143.12, 140.28, 133.90, 127.22, 124.83, 117.49, 111.74, 73.29, 71.04, 67.06, 58.89, 56.72, 56.48, 46.11, 45.66, 43.28, 40.94, 40.72, 29.34, 28.24, 27.84, 27.41, 23.93, 22.63, 21.23, 12.33, 11.67, 6.11, 2.54.

Example IV

Preparation of compound 27a from compound 8.

The reaction equations are presented in the Reaction Scheme B appended. Vitamin D compound 27a is prepared from compound 8, via the intermediate compounds 11, 15, 19, 23 and 27, analogous to the reaction sequence described in Example II for the first 5 steps. During the fifth step (deprotection step) ring closure takes place between the deprotected aldehyde group of the 24-substituent and the free 25-OH group, forming compound 27. Compound 27 can easily be converted to the corresponding alcohol 27a by ring-opening and reduction of the aldehyde group.

Compound 11 is identified by ¹H-NMR and ¹³C-NMR:

¹H-NMR: 5.22 (1H, dd, J=15.2 and 8.5 Hz, H-22 or H-23), 5.04 (1H, dd, J=15.2 and 9.2 Hz, H-23 or H-22), 4.83 (1H, t, J=4.5 Hz, OCHRO), 4.72 (2H, AB, J=7.4 Hz, OCH₂O), 3.96 (1H, s, H-8), 3.96-3.78 (4H, m, OCH₂CH₂O), 3.34 (3H, s, OCH₃), 1.16 (3H, s, CH₃-26 or 27), 1.11 (3H, s, CH₃-26 or 27), 0.96 (3H, d, J=6.57 Hz, CH₃-21), 0.90 (3H, s, CH₃-

18), 0.87 (9H, s, SiC(CH₃)₃), -0.01 (3H, s, SiCH₃), -0.03 (3H, s, SiCH₃).
¹³C-NMR: 140.33 (C=), 127.58 (C=), 104.91 (OCHRO), 90.89 (OCH₂O), 78.10 (C-25), 69.45, 64.78 (OCH₂CH₂O), 64.73 (OCH₂CH₂O), 56.41, 55.09, 53.25, 53.10, 41.99 (C-13), 40.62 (CH₂), 39.94, 34.39 (CH₂), 32.46 (CH₂), 27.93 (CH₂), 25.73 (SiC(CH₃)₃), 25.47, 23.14 (CH₂), 23.03 (CH₂), 22.94, 20.56, 17.93 (SiC(CH₃)₃), 17.60, (CH₂), 13.83, -4.91 (SiCH₃), -5.28 (SiCH₃).

Compound 27 is identified by ¹H-NMR and ¹³C-NMR:

¹H-NMR (δ, CD₂Cl₂): 6.33 (1H, d, J=11.2 Hz), 5.99 (1H, d, J=11.2 Hz), 5.30-5.26 (1H, m), 5.27 (1H, s), 5.12 (1H, dd, J=15.3 Hz and 8.4 Hz), 4.93 (1H, s), 4.60 (0.375 H, d, J=1.4 Hz), 4.44 (0.625 H, dd, J=9.5 and 2.4 Hz), 4.35 (1H, m), 4.14 (1H, m), 3.34 (1.875 H, s), 3.32 (1.125 H, s), 2.82 (1H, d, J=12.4 Hz), 2.52 (1H, dd, J=13.4 and 3.5 Hz), 2.25 (1H, dd, J=13.4 and 6.6 Hz), 1.17 (3H, s), 1.12 (1.125 H, s), 1.08 (1.875 H, s), 0.99 (3H, d, J=6.6 Hz), 0.53 (3H, s).
¹³C-NMR (δ, CD₂Cl₂): 148.45, 143.01, 142.98, 138.77, 138.19, 134.02, 133.99, 129.05, 128.46, 124.76, 117.53, 111.70, 99.08, 98.41, 76.26, 75.47, 70.95, 67.03, 56.70, 56.65, 55.59, 55.14, 49.12, 48.68, 46.13, 45.63, 43.32, 40.77, 40.72, 40.69, 31.53, 30.40, 29.74, 29.70, 29.35, 28.05, 25.91, 23.92, 23.35, 22.58, 22.11, 20.99, 19.66, 12.34.

Example V

Preparation of compound 28 from compound 8.

The reaction equations are presented in the Reaction Scheme B appended. Via a reaction sequence analogous to that described in Example II, Vitamin D compound 28 is prepared from compound 8, via the intermediate compounds 12, 16, 20 and 24.

Compound 12 is identified by ¹H-NMR and ¹³C-NMR:

¹H-NMR: 5.23 (1H, dd, J=15.2 and 9.36 Hz, H-22 or H-23), 5.13 (1H, dd, J=15.2 and 8.3 Hz, H-22 or H-23), 4.68 (2H, s, OCH₂O), 3.99 (1H, s, H-8), 3.35 (3H, s, OCH₃), 1.17 (6H, s, CH₃-26 and 27), 0.99 (3H, d, J=6.55 Hz, CH₃-21), 0.93 (3H, 9, CH₃-18), 0.88 (9H, 9, SiC(CH₃)₃), 0.87 and 0.84 (6H, 2d, J=3.5 and 3.4 Hz, CH(CH₃)₂), 0.00 (3H, s, SiCH₃), -0.01 (3H, s, SiCH₃).
¹³C-NMR: 140.65 (C=), 124.53 (C=), 90.84 (OCH₂O), 78.69 (C-25), 69.49, 58.64, 56.48, 55.05, 53.20, 42.00 (C-13), 40.69 (CH₂), 40.35, 34.45 (CH₂), 28.38 (CH₂), 26.75, 26.15, 25.77 (SiC(CH₃)₃), 24.48, 24.09, 23.19 (CH₂), 20.71, 18.96, 17.96 (SiC(CH₃)₃), 17.64 (CH₂), 13.88, -4.89 (SiCH₃), -5.25 (SiCH₃).

Compound 28 is identified by ¹H-NMR and ¹³C-NMR:

¹H-NMR (δ, CD₂Cl₂): 6.34 (1H, d, J=11.2 Hz), 6.00 (1H, d, J=11.2 Hz), 5.30-5.27 (2H, m), 5.26 (1H, s), 4.94 (1H, dd, J=1.2 and 1.8 Hz), 4.36 (1H, m), 4.14 (1H, m), 2.82 (1H, d, J=12.3 Hz), 2.54 (1H, dd, J=3.5 and 13.4 Hz), 2.25 (1H, dd, J=6.6 and 13.4 Hz), 1.14 (3H, s), 1.04 (3H, d, J=6.6 Hz), 0.86 (6H, d, J=6.9 Hz), 0.56 (3H, s).
¹³C-NMR (δ, CD₂Cl₂): 148.43, 1543.13, 142.30, 133.86, 124.85, 124.68, 117.48, 111.69, 72.95, 71.06, 67.08, 60.30, 56.74, 56.54, 46.13, 45.69, 43.32, 41.27, 40.74, 29.34, 28.75, 28.57, 28.38, 27.70, 24.39, 23.93, 22.67, 21.26, 19.00, 12.27.

Example VI

Preparation of compound 30 from compound 17.

The reaction equations are presented in the Reaction Scheme B appended.

(a). The preparation of protected 19-nor-vitamin D compound 29.

To a solution of the phosphine-oxide 46 (360 mg, 0.63 mmol) in 5 ml dry THF at -78°C is added a small amount of n-BuLi in THF (2.5 M, approx. 230 μl) until the reaction mixture colours red. Thereupon n-BuLi in THF (2.5 M, 254 μl, 0.63 mmol) is added dropwise. After stirring for 5 min, a solution of 80.1 mg (0.21 mmol) of compound 17 in 2 ml dry THF is added. The mixture is stirred for 0.5 h and allowed to reach room temp. Purification by chromatography yields 106.7 mg (69%) of the desired title compound 29.

(b). The preparation of 19-nor-vitamin D compound 30.

Compound 29 (103 mg, 0.139 mmol) is dissolved in a 0.83 M solution of TBAF (3.4 ml, 2.78 mmol, 20 eq.) in THF. The mixture is stirred overnight at ambient temperature. The solvent is evaporated and the residue is taken up with Et₂O and washed with brine. The organic phase is dried over MgSO₄ and the solvent evaporated. The residue is quickly chromatographed over silica (Et₂O) and the resulting product is dissolved in methanol (10 ml) and 1.75 g of Dowex[®] resin (acidic resin) AG 50W-X4 (washed with MeOH (4x12 ml)) is added. After stirring overnight, filtration and washing with EtOAc (3x20 ml), the reaction mixture is evaporated. The desired 19-nor-vitamin D compound 30 is obtained in a yield of 30 mg as a white solid. The product is identified by ¹H-NMR

and ^{13}C -NMR.

^1H -NMR (δ , CDCl_3): 0.36 (3H, s, 18- CH_3), 0.87 (3H, t, CH_3), 1.05 (3H, d, 21- CH_3), 1.12 (3H, s, 26- CH_3), 1.17 (3H, s, 27- CH_3), 2.48 (1H, dd), 2.71 (1H, dd), 2.80 (1H, bd), 4.00-4.16 (2H, m), 5.10 (1H, dd, 22-H), 5.37 (dd, 23-H), 5.85 (1H, d, H-6), 6.31 (1H, d, H-7).

^{13}C -NMR: 12.32, 14.10, 21.20, 22.35, 22.55, 23.47, 26.80, 26.99, 28.07, 28.91, 29.19, 30.40, 37.20, 40.36, 40.67, 42.21, 44.71, 45.70, 54.85, 56.19, 56.35, 67.22, 67.43, 72.14, 115.37, 123.80, 128.00, 131.26, 141.49, 142.87.

Example VII

Preparation of compound 30 and 31 from compound 8.

The reaction equations are presented in the Reaction Scheme C appended.

A solution of phenylmagnesiumchloride in THF (2M, 15 ml, 30 mmol) is added to a solution of CuCN (2.69 g, 30 mmol) and LiCl (2.54 g, 40 mmol) in 40 ml THF while stirring and cooling at -78°C . The reaction mixture is stirred for 5 min and a solution of phosphate 8 (897 mg, 1.518 mmol, dried over P_2O_5) in 15 ml THF is added. The reaction is stirred for 2 days under exclusion of light. To the reaction mixture is added a saturated solution of NH_4Cl (100 ml). After stirring for 10 min, the mixture is extracted at room temp with Et_2O (3x60 ml). The combined organic layers are dried, filtered and concentrated. The residue is separated by chromatography over silica gel (eluent: 0-1.5% EtOAc /hexane), yielding 173 mg of compound 30 [22%, $R_f=0.52$ (5% EtOAc /hexane), liquid], and 591 mg of compound 31 [76%, $R_f=0.46$ (5% EtOAc /hexane), m.p. $71-72^\circ\text{C}$]. The compounds 30 and 31 are identified by ^1H -NMR and ^{13}C -NMR.

Compound 30: ^1H -NMR (δ): 7.26-7.17 (5H, m, Ar), 5.83 (1H, dd, $J=15.3$ and 8.8 Hz, H-23), 5.28 (1H, dd, $J=15.3$ and 8.4 Hz, H-22), 4.69 (2H, AB, $J=7.4$ Hz, OCH_2O), 3.96 (1H, s, H-8), 3.30 (3H, s, OCH_3), 3.20 (1H, d, $J=8.8$ Hz, H-24), 1.21 (3H, s, CH_3 -26 or 27), 1.15 (3H, s, CH_3 -26 or 27), 1.00 (3H, d, $J=6.59$ Hz, CH_3 -21), 0.91 (3H, s, CH_3 -18), 0.88 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.00 (3H, s, SiCH_3), -0.02 (3H, s, SiCH_3).

^{13}C -NMR (δ): 142.65 (C), 139.25 (C=), 129.70 (C=), 127.60 (C=), 127.19 (C=), 125.95 (C=), 91.01 (OCH_2O), 78.08 (C-25), 69.44, 59.89, 56.66, 54.95, 53.04, 42.03 (C-13), 40.62 (CH_2), 39.77, 34.40 (CH_2), 27.58 (CH_2), 25.75 ($\text{Si}(\text{CH}_3)_3$), 25.02, 24.98, 23.01 (CH_2), 20.26, 17.93 ($\text{Si}(\text{CH}_3)_3$), 17.61 (CH_2), 13.83, -4.90 (SiCH_3), -5.27 (SiCH_3).

Compound 31: ^1H -NMR (δ): 7.31-7.15 (5H, m, Ar), 5.92 (1H, dd, $J=15.7$ and 10.1 Hz, H-23), 5.60 (1H, d, $J=15.7$ Hz, H-24), 4.67 (2H, s, OCH_2O), 4.00 (1H, s, H-8), 3.51 (1H, d, $J=10.1$ Hz, H-22), 3.36 (3H, s, OCH_3), 1.39 (3H, s, CH_3 -26 or 27), 1.37 (3H, s, CH_3 -26 or 27), 0.94 (3H, s, CH_3 -18), 0.89 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.76 (3H, d, $J=6.76$ Hz, CH_3 -21), 0.01 (6H, s, $\text{Si}(\text{CH}_3)_2$).

^{13}C -NMR (δ): 145.22 (C), 138.09 (C=), 128.08 (C=), 127.92 (C=), 127.43 (C=), 125.64 (C=), 91.92 (OCH_2O), 76.24 (C-25), 69.44, 54.97, 53.10, 50.01, 48.54, 42.03, 40.71 (CH_2), 34.31 (CH_2), 27.91, 27.26 (CH_2), 27.22, 25.76 ($\text{Si}(\text{CH}_3)_3$), 23.04 (CH_2), 17.96 ($\text{Si}(\text{CH}_3)_3$), 17.55 (CH_2), 13.72, 13.29, -4.87 (SiCH_3), -5.25 (SiCH_3).

Example VIII

Preparation of compound 36 from compound 30.

The reaction equations are presented in the Reaction Scheme C appended.

Via a reaction sequence analogous to that described in Example II, Vitamin D compound 36 is prepared from compound 30, via the intermediate compounds 33, 34 and 35.

Compound 36 is identified by ^1H -NMR and ^{13}C -NMR:

^1H -NMR (δ , CD_2Cl_2): 7.29-7.18 (5H, m), 6.33 (1H, d, $J=11.2$ Hz), 5.98 (1H, d, $J=11.2$ Hz), 5.82 (1H, dd, $J=15.2$ and 9.4 Hz), 5.42 (1H, dd, $J=15.2$ and 8.5 Hz), 5.26 (1H, s), 4.92 (1H, dd, $J=2.0$ and 1.2 Hz), 4.34 (1H, m), 4.14 (1H, m), 3.18 (1H, d, $J=9.5$ Hz), 1.13 (3H, s), 1.10 (3H, s), 1.06 (3H, d, $J=6.6$ Hz), 0.53 (3H, s).

^{13}C -NMR (δ , CD_2Cl_2): 148.41, 142.99, 142.44, 140.46, 133.96, 129.58, 128.32, 127.19, 126.62, 124.78, 117.52, 111.784, 72.69, 71.00, 67.03, 60.72, 56.62, 46.17, 45.65, 43.29, 40.70, 40.66, 31.93, 29.33, 28.13, 27.99, 27.80, 23.91, 23.00, 22.56, 20.86, 14.23, 12.29.

Example IX

Preparation of compound 43 from compound 31.

The reaction equations are presented in the Reaction Scheme C appended.

Via a reaction sequence analogous to that described in Example II, Vitamin D compound 43 is prepared from compound 31, via the intermediate compounds 37, 39 and 41.

Compound 43 is identified by ^1H -NMR and ^{13}C -NMR:

¹H-NMR (δ, CD₂Cl₂): 7.27-7.14 (5H, m), 6.35 (1H, d, J=11.2 Hz), 6.03 (1H, d, J=11.2 Hz), 5.89 (1H, dd, J=15.8 and 10.3 Hz), 5.55 (1H, d, J=15.8 Hz), 5.29 (1H, d, J=1.4 Hz), 4.96 (1H, s), 4.36 (1H, m), 4.15 (1H, m), 3.5 (1H, d, J=10.3 Hz), 2.80 (1H, d, J=12 Hz), 2.52 (1H, d, J=13 Hz), 2.25 (1H, dd, J=13 and 6.5 Hz), 1.29 (3H, s), 1.27 (3H, s), 0.80 (3H, d, J=6.8 Hz), 0.57 (3H, s).

¹³C-NMR (δ, CD₂Cl₂): 148.43, 145.66, 142.99, 138.69, 133.96, 128.33, 128.27, 127.51, 125.92, 124.84, 117.61, 111.76, 75.20, 71.08, 67.08, 56.74, 55.13, 50.67, 50.50, 46.14, 45.68, 43.34, 43.20, 40.90, 29.32, 27.97, 26.78, 25.77, 23.89, 22.64, 13.69, 12.11.

Example X

Preparation of compound 44 from compound 8.

The reaction equations are presented in the Reaction Scheme C appended.

(a). Preparation of compound 32.

A solution of vinylmagnesiumchloride in THF (15%, 5.08 ml, 8.6 mmol) is added to a solution of CuCN (770 mg, 8.6 mmol) and LiCl (729 mg, 17.2 mmol) in 20 ml THF while stirring and cooling at -78°C. The reaction mixture is stirred for 5 min and a solution of phosphate 8 (497 mg, 0.841 mmol, dried over P₂O₅) in 20 ml THF is added. The reaction is stirred for 3 days under exclusion of light. To the reaction mixture is added a satd. solution of NH₄Cl (25 ml). After stirring for 5 min, the mixture is extracted at room temp with Et₂O (3x20 ml). The combined organic layers are dried, filtered and concentrated. The residue is chromatographed over silica gel (eluent: 2-30% EtOAc/hexane), yielding 225 mg of compound 32 [58%, R_f=0.8 (10% EtOAc/hexane), crystallizing upon cooling, m.p. 30°C], whereas 61 mg of starting compound 8 is recovered. Compound 32 is identified by ¹H-NMR and ¹³C-NMR.

¹H-NMR (δ): 5.83 (1H, ddd, J=17.3, 10.4 and 5.3 Hz, CH=CH₂), 5.57-5.44 (2H, m, H-23 and H-24), 5.01 (1H, dt, J_{cis}=10.4 Hz, J_{gem}=1.8 Hz, C=CHH), 4.91 (1H, dt, J_{trans}=17.3 Hz, J_{gem}=1.8 Hz, C=CHH), 4.65 (2H, s, OCH₂O), 3.98 (1H, s, H-8), 3.35 (3H, s, OCH₃), 2.86 (1H, s, H-22), 1.34 (6H, s, CH₃-26 and 27), 0.92 (3H, s, CH₃-18), 0.88 (H, s, SiC(CH₃)₃), 0.84 (3H, d, J=6.81 Hz, CH₃-21), 0.00 (3H, s, SiCH₃), -0.01 (3H, s, SiCH₃).

¹³C-NMR (δ): 142.31 (C=), 137.57 (C=), 127.93 (C=), 114.31 (=CH₂), 91.86 (OCH₂O), 76.20 (C-25), 69.43, 54.96, 54.73, 53.01, 48.54, 42.01 (C-13), 40.72 (CH₂), 40.35, 34.33 (CH₂), 27.82, 27.24, 26.90 (CH₂), 25.74 (SiC(CH₃)₃), 23.00 (CH₂), 17.94 (SiC(CH₃)₃), 17.56 (CH₂), 13.86, 13.69, -4.89 (SiCH₃), -5.27 (SiCH₃).

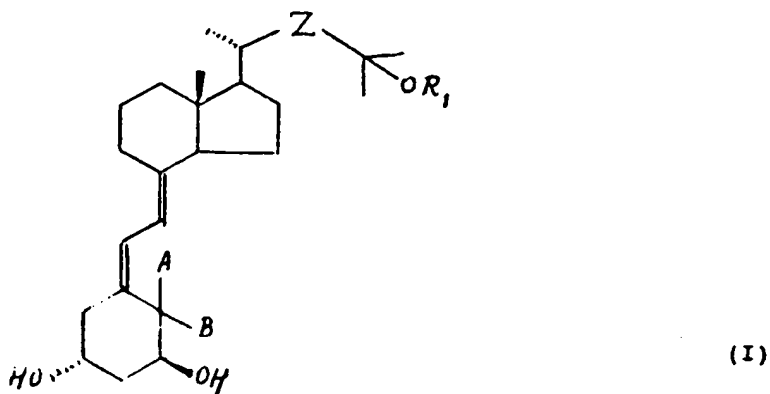
Via a reaction sequence analogous to that described in Example II, Vitamin D compound 44 is prepared from compound 32, via the intermediate compounds 38, 40 and 42.

Compound 44 is identified by ¹H-NMR and ¹³C-NMR:

¹H-NMR (δ, CD₂Cl₂): 6.33 (1H, d, J=11.2 Hz), 6.00 (1H, d, J=11.2 Hz), 5.85 (1H, ddd, J=17.2, 10.4 and 5.7 Hz), 5.48 (1H, dd, J=15.9 and 8.4 Hz), 5.42 (1H, d, J=15.9 Hz), 5.28 (1H, t, J=1.6 Hz), 5.00 (1H, dt, J=10.4 and 1.8 Hz), 4.94 (1H, s), 4.93 (1H, dt, J=17.2 and 1.8 Hz), 4.35 (1H, m), 4.14 (1H, m), 2.85 (1H, m), 2.82 (1H, d, J=12 Hz), 2.53 (1H, dd, J=13 and 2.6 Hz), 2.25 (1H, dd, J=13.2 and 6.6 Hz), 1.24 (3H, s), 1.33 (3H, s), 0.87 (3H, d, J=6.8 Hz), 0.55 (3H, s). ¹³C-NMR (δ, CD₂Cl₂): 148.41, 143.06, 142.83, 138.19, 133.90, 127.95, 124.85, 117.54, 114.32, 111.77, 75.16, 71.09, 67.07, 56.63, 54.88, 50.39, 49.19, 46.08, 45.69, 43.33, 41.54, 40.89, 29.33, 27.63, 26.64, 25.84, 23.91, 22.60, 14.26, 12.08.

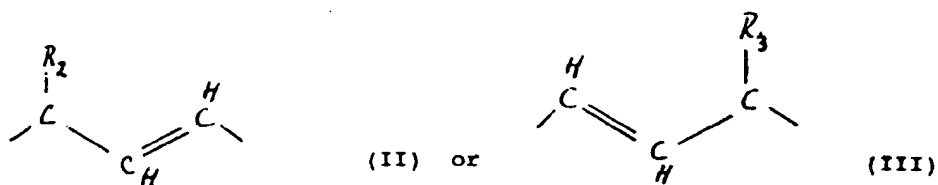
Claims

1. A vitamin D compound of the general formula



wherein:

R_1 is a hydrogen atom or a hydroxy protecting group;
 Z is a group of the general formula

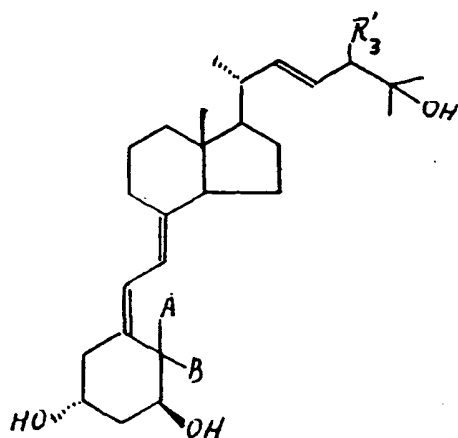


wherein

R_2 and R_3 are each individually straight or branched (C_1 - C_6)alkyl groups or (C_2 - C_6)alkenyl groups, optionally substituted with one or more substituents selected from hydroxy, (C_1 - C_4)alkoxy, fluoro, (C_3 - C_6) cycloalkyl and (C_2 - C_3)alkylenedioxy; or with unsubstituted or substituted phenyl; or (C_3 - C_6)cycloalkyl groups, or unsubstituted or substituted phenyl groups; or wherein R_1 and R_3 together with the interconnecting oxadimethylene biradical form a 5-7 membered ring-closed (C_1 - C_4)alkyl substituted hemiacetal; with the proviso, that R_2 and R_3 are not methyl groups;

A and B are each individually hydrogen atoms or methyl groups, or
 A and B form together a methylene group.

2. A vitamin D compound as claimed in Claim 1, having the general formula

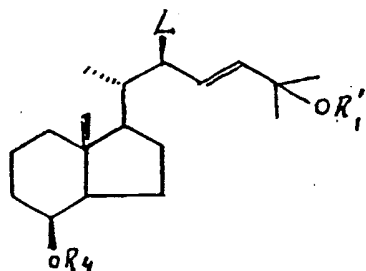


(IV)

wherein:

A and B have the meanings given in Claim 1, and R_3' is a straight or branched (C_2 - C_6) alkyl group, optionally substituted with hydroxy, (C_1 - C_2) alkoxy or (C_2 - C_3) alkylenedioxy, a cyclopropyl group or a phenyl group.

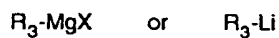
3. A vitamin D compound as claimed in Claim 2, having the general formula IV, shown in Claim 2, wherein the symbols have the meanings given in Claim 2, on the understanding that C-24, to which substituent R_3' is attached, has either the R or the S configuration.
4. A method of preparing a vitamin D compound as claimed in Claim 1, characterized in that a hydrindane compound of the general formula



(V)

wherein:

L is a leaving group, and R_1' and R_4 are each individually hydroxy-protecting groups; is reacted with a reagent of the general formula

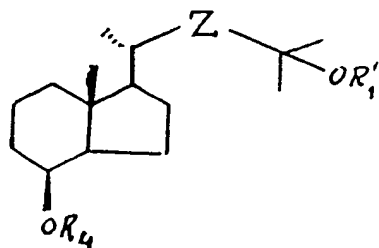


wherein:

R_3 has the meaning given in Claim 1, and X is a halogen atom,

in the presence of a Cu(I) compound;

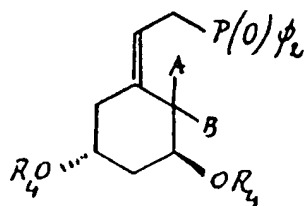
after which the hydrindane intermediate obtained, having the general formula



(VI)

wherein Z has the meaning given in Claim 1,
is oxidized, after deprotection of OR_4 , to the corresponding hydrindane-4-one compound, and is then converted,
in a manner known per se for related compounds,

either (a) with a Wittig reagent of the general formula

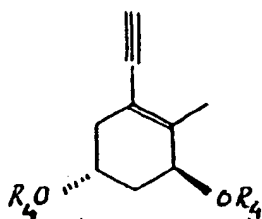


(VII)

wherein:

R_4 has the above meaning, and
A and B have the meanings given in Claim 1,

or (b), after enolization, with an enyne compound of the general formula

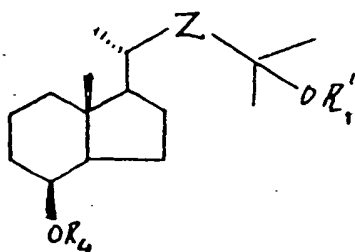


(VIII)

wherein R_4 has also the above meaning, followed by hydrogenation and isomerization, to produce a compound
of the general formula I, wherein A and B form together a methylene group;

followed by deprotection.

5. A hydrindane intermediate which can be used in the method of Claim 4 and which has the general formula

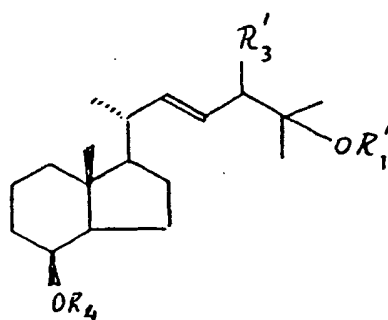


(VI)

wherein:

Z has the meaning given in Claim 1, and
 R_1' and R_4 have the meanings given in Claim 4.

6. A hydrindane intermediate as claimed in claim 5, having the general formula

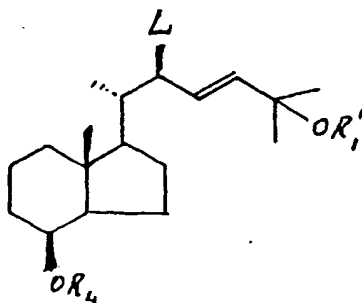


(IX)

wherein:

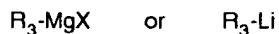
R_3' has the meaning given in Claim 2, and
 R_1' and R_4 have the meanings given in Claim 4.

7. A hydrindane intermediate as claimed in Claim 6, having the general formula IX, wherein the C-atom, to which substituent R_1' is attached, has either the *R* or the *S* configuration.
8. A method of preparing a hydrindane intermediate as claimed in Claim 5, characterized in that a compound of the general formula VI, shown in Claim 5, wherein the symbols have the meanings given in Claim 5, is prepared by reacting a hydrindane compound of the general formula



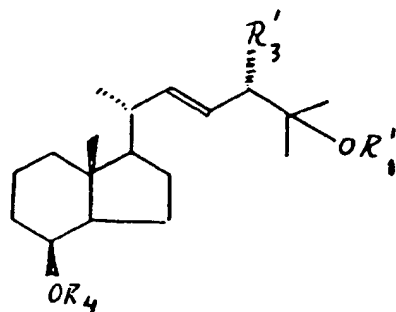
(V)

wherein L, R₁' and R₄ have the meanings given in Claim 4;
with a reagent of the general formula



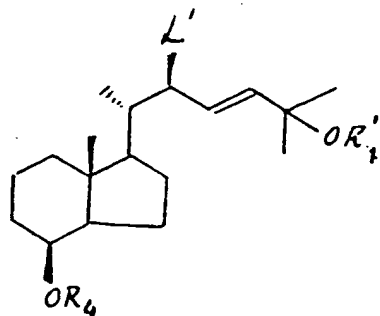
wherein R₃ has the meaning given in Claim 1 and X is a halogen atom, in the presence of a Cu(I) compound.

9. A method as claimed in Claim 8, characterized in that a compound of the general formula IX is prepared, wherein the C-atom, to which substituent R₃' is attached, has the configuration of formula IXA



(IXA)

by reacting a hydrindane compound of the general formula

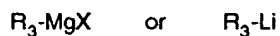


(X)

wherein:

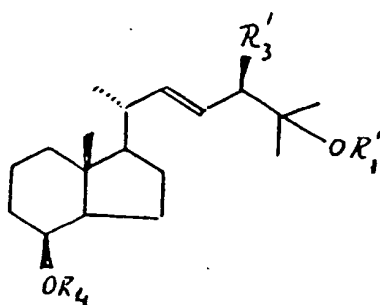
R₁' and R₄ have the meanings given in Claim 4, and
L' is a di(hydrocarbyl)phosphate leaving group;

with a reagent of the general formula



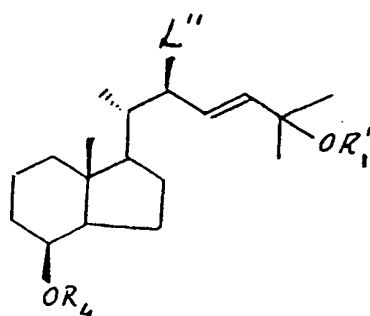
wherein R₃ has the meaning given in Claim 1 and X is a halogen atom,
in the presence of a Cu(I) compound.

10. A method as claimed in Claim 8, characterized in that a compound of the general formula IX is prepared, wherein the C-atom, to which substituent R₃' is attached, has the configuration of formula IXB



(IXB)

by reacting a hydrindane compound of the general formula

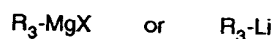


(XI)

wherein:

R_1' and R_4 have the meanings given in Claim 4, and
 L'' is a N-arylcarbamate leaving group;

with a reagent of the general formula

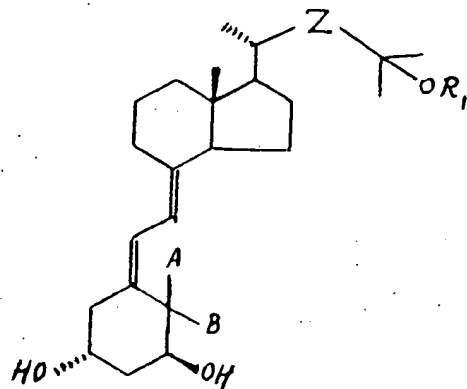


wherein R_3 has the meaning given in Claim 1 and X is a halogen atom, in the presence of a Cu(I) compound.

11. A pharmaceutical composition comprising, in addition to a pharmaceutically acceptable carrier and/or at least one pharmaceutically acceptable auxiliary substance, as the active ingredient at least one compound as defined in Claim 1, 2 or 3 in an effective amount.
12. A composition as claimed in claim 11 when for use in a method for treatment and/or prevention of a number of skin disorders or of a number of diseases, including bone diseases such as osteoporosis, renal osteodystrophy and osteomalacia, autoimmune diseases, acne, alopecia, skin aging, imbalance in the immune system, inflammatory diseases such as rheumatoid arthritis and asthma, as well as diseases related to abnormal cell differentiation and/or proliferation, as well as solid, skin or blood cancers, in a warm-blooded living being, comprising administering to said being or treating said being with a composition as claimed in Claim 11 in a quantity effective for the intended purpose.

Patentansprüche

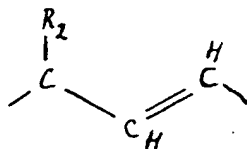
1. Vitamin D-Verbindung der allgemeinen Formel



(I),

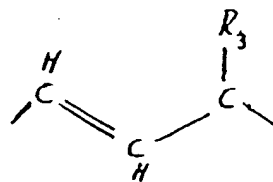
worin:

R_1 ein Wasserstoffatom oder eine Hydroxy-Schutzgruppe bedeutet;
 Z eine Gruppe darstellt der allgemeinen Formel



(II)

oder

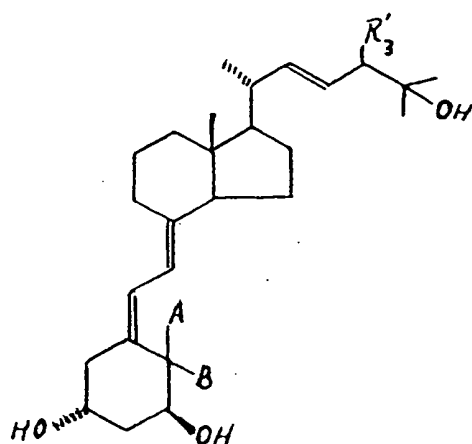


(III)

worin R_2 und R_3 jeweils einzeln bedeuten: gerade oder verzweigte (C_1 - C_6) Alkyl-Gruppen oder (C_2 - C_6) Alkenyl-Gruppen,
 gegebenenfalls substituiert mit einem oder mehreren Substituenten, ausgewählt aus Hydroxy, (C_1 - C_4) Alkoxy, Fluor, (C_3 - C_6) Cycloalkyl und (C_2 - C_3) Alkylendioxy; oder mit unsubstituiertem oder substituiertem Phenyl;
 oder (C_3 - C_6) Cycloalkyl-Gruppen, oder unsubstituierte oder substituierte Phenyl-Gruppen;
 oder worin R_1 und R_3 zusammen mit dem sie verbindenden Oxadimethylenbirest einen 5- bis 7-gliedrigen, im Ring geschlossenen (C_1 - C_4) Alkyl-substituierten Hemiacetal bilden;
 mit der Maßgabe, daß R_2 und R_3 keine Methyl-Gruppen sind;

A und B jeweils einzeln Wasserstoffatome oder Methyl-Gruppen bedeuten, oder A und B zusammen eine Methylen-Gruppe bilden.

2. Vitamin D-Verbindung nach Anspruch 1 der allgemeinen Formel

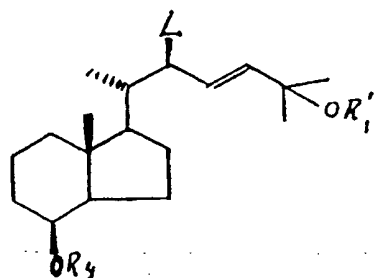


(IV),

worin:

A und B die in Anspruch 1 angegebenen Bedeutungen haben, und R_3' darstellt: eine gerade oder verzweigte (C_2 - C_6) Alkyl-Gruppe, gegebenenfalls substituiert mit Hydroxy, (C_1 - C_2) Alkoxy oder (C_2 - C_3) Alkylendioxy, einer Cyclopropyl-Gruppe oder einer Phenyl-Gruppe.

3. Vitamin D-Verbindung nach Anspruch 2 der in Anspruch 2 gezeigten allgemeinen Formel (IV), worin die Symbole die in Anspruch 2 angegebenen Bedeutungen haben, mit der Maßgabe, daß C-24, an welchen Substituenten R_3' gebunden ist, entweder R- oder S-Konfiguration aufweist.
4. Verfahren zur Herstellung einer Vitamin D-Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß eine Hydrindan-Verbindung der allgemeinen Formel

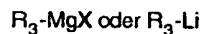


(V),

worin:

L eine Abgangsgruppe bedeutet, und R_1' und R_4 jeweils einzeln Hydroxy-Schutzgruppen darstellen;

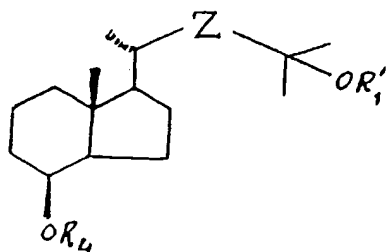
umgesetzt wird mit einem Reagenz der allgemeinen Formel



worin:

R_3 die in Anspruch 1 angegebene Bedeutung hat, und X ein Halogenatom darstellt, in Anwesenheit einer Cu(I)-Verbindung;

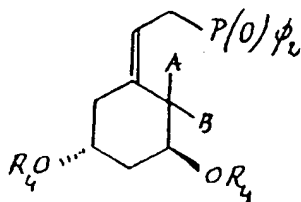
wonach die erhaltene Hydrindan-Zwischenverbindung der allgemeinen Formel



(VI),

worin Z die in Anspruch 1 angegebene Bedeutung hat;
nach Entschützen von OR_4 , zur entsprechenden Hydrindan-4-on-Verbindung oxidiert wird, und dann auf an
sich für verwandte Verbindungen bekannte Weise übergeführt wird

entweder (a) mit einem Wittig-Reagenz der allgemeinen Formel

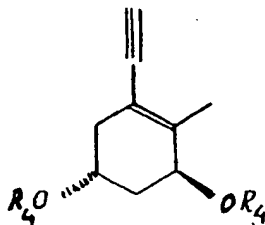


(VII),

worin:

R_4 die obige Bedeutung hat, und
A und B die in Anspruch 1 angegebenen Bedeutungen haben;

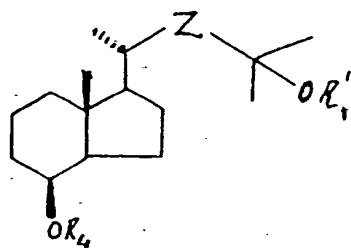
oder (b), nach Enolisierung, mit einer Enyn-Verbindung der allgemeinen Formel



(VIII),

worin R_4 auch die obige Bedeutung hat, gefolgt von Hydrierung und Isomerisierung, zur Herstellung einer
Verbindung der allgemeinen Formel (I), worin A und B zusammen eine Methylen-Gruppe bilden; gefolgt von
Entschützen.

5. Hydrindan-Zwischenverbindung, welche im Verfahren nach Anspruch 4 verwendet werden kann, und welche die
allgemeine Formel aufweist:

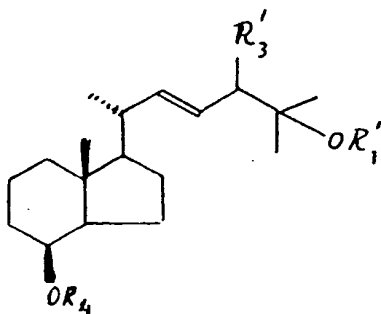


(VI),

worin:

Z die in Anspruch 1 angegebene Bedeutung hat, und
 R_1' und R_4 die in Anspruch 4 angegebenen Bedeutungen haben.

6. Hydrindan-Zwischenverbindung nach Anspruch 5 der allgemeinen Formel

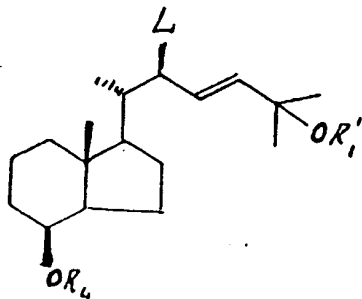


(IX),

worin:

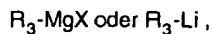
R_3' die in Anspruch 2 angegebene Bedeutung hat, und
 R_1' und R_4 die in Anspruch 4 angegebenen Bedeutungen haben.

7. Hydrindan-Zwischenverbindung nach Anspruch 6 der allgemeinen Formel (IX), worin das C-Atom, an das der Substituent R_1' gebunden ist, eritweder R- oder S-Konfiguration aufweist.
8. Verfahren zur Herstellung einer Hydrindan-Zwischenverbindung nach Anspruch 5, dadurch gekennzeichnet, daß eine Verbindung der in Anspruch 5 gezeigten allgemeinen Formel (VI), worin die Symbole die in Anspruch 5 angegebenen Bedeutungen haben, hergestellt wird durch das Umsetzen einer Hydrindan-Verbindung der allgemeinen Formel



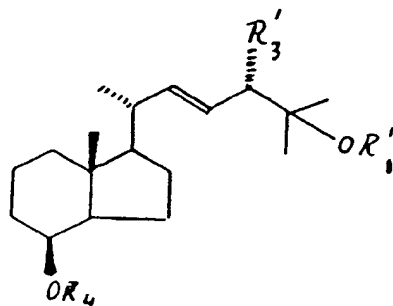
(V),

worin L, R₁' und R₄ die in Anspruch 4 angegebenen Bedeutungen haben; mit einem Reagenz der allgemeinen Formel



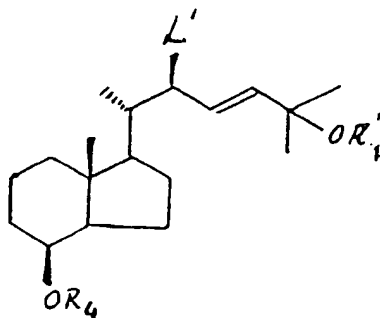
worin R₃ die in Anspruch 1 angegebene Bedeutung hat, und X ein Halogenatom darstellt, in Anwesenheit einer Cu(I)-Verbindung.

9. Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß eine Verbindung der allgemeinen Formel (IX) hergestellt wird, worin das C-Atom, an das der Substituent R₃' gebunden ist, die Konfiguration der Formel (IXA)



(IXA)

aufweist, durch das Umsetzen einer Hydrindan-Verbindung der allgemeinen Formel



(X),

worin:

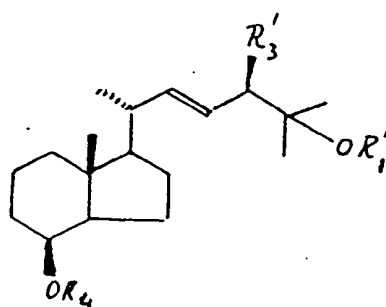
R₁' und R₄ die in Anspruch 4 angegebenen Bedeutungen haben, und L' eine Di-(hydrocarbyl)-phosphat-Abgangsgruppe darstellt;

mit einem Reagenz der allgemeinen Formel



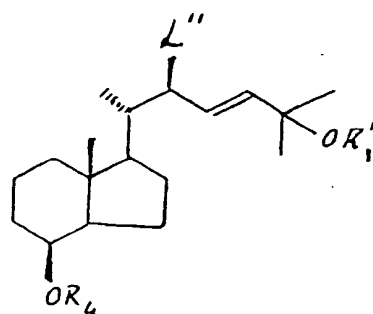
worin R₃ die in Anspruch 1 angegebene Bedeutung hat, und X ein Halogenatom darstellt, in Anwesenheit einer Cu(I)-Verbindung.

10. Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß eine Verbindung der allgemeinen Formel (IX) hergestellt wird, worin das C-Atom, an das der Substituent R₃' gebunden ist, die Konfiguration der Formel (IXB)



(IXB)

aufweist, durch das Umsetzen einer Hydrindan-Verbindung der allgemeinen Formel

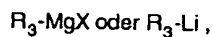


(XI),

worin:

R_1' und R_4 die in Anspruch 4 angegebenen Bedeutungen haben, und L'' eine N-Arylcarbamat-Abgangsgruppe darstellt;

mit einem Reagenz der allgemeinen Formel



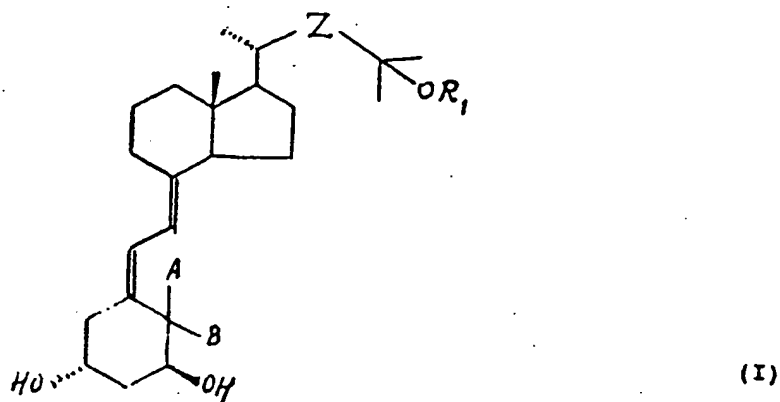
worin R_3 die in Anspruch 1 angegebene Bedeutung hat, und X ein Halogenatom darstellt, in Anwesenheit einer Cu(I)-Verbindung.

11. Pharmazeutische Zusammensetzung, welche, zusätzlich zu einem pharmazeutisch annehmbaren Träger und/oder zumindest einer pharmazeutisch annehmbaren Hilfssubstanz, als aktiven Bestandteil zumindest eine wie in Anspruch 1, 2 oder 3 definierte Verbindung in einer wirksamen Menge umfaßt.

12. Zusammensetzung nach Anspruch 11, wenn sie zur Verwendung in einem Verfahren zur Behandlung und/oder Prävention einer Reihe von Hautkrankheiten oder einer Reihe von Erkrankungen dient, einschließlich Knochenkrankheiten, wie Osteoporose, renale Osteodystrophie, Osteodystrophie und Osteomalazie, Autoimmunkrankheiten, Akne, Alopezie, Hautalterung, Ungleichgewicht des Immunsystems, entzündliche Erkrankungen, wie rheumatoide Arthritis und Asthma, sowie Krankheiten, die mit abnormaler Zelldifferenzierung und/oder Proliferation in Zusammenhang stehen, sowie feste Tumoren, Haut- oder Blutkrebs, bei einem warmblütigen Lebewesen, umfassend die Verabreichung einer Zusammensetzung nach Anspruch 11 in einer für den beabsichtigten Zweck wirksamen Menge an das Lebewesen oder Behandeln des Lebewesens damit.

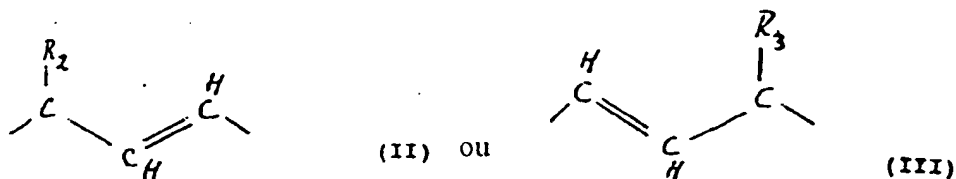
Revendications

1. Composé de vitamine D de formule générale



dans laquelle :

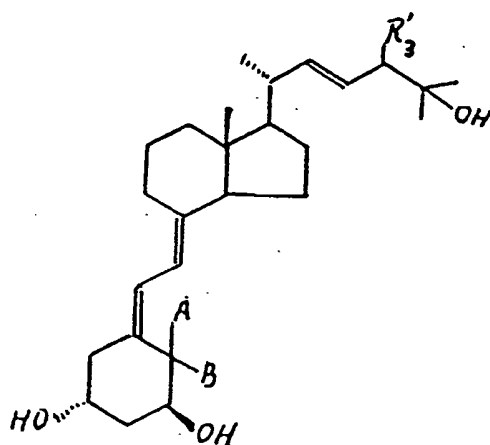
R_1 est un atome d'hydrogène ou un groupe protégeant un groupe hydroxy ;
 Z est un groupe de formule générale



dans lesquelles R_2 et R_3 sont chacun individuellement des groupes alkyles en C_1 à C_6 ou groupes alcényles en C_2 à C_6 linéaires ou ramifiés, éventuellement substitués par un ou plusieurs substituants choisis parmi les radicaux hydroxy, alcoxy en C_1 à C_4 , fluoro, cycloalkyles en C_3 à C_6 et alkylènedioxy en C_2 à C_3 ; ou par un groupe phényle non substitué ou substitué ;
 ou bien des groupes cycloalkyles en C_3 à C_6 , ou des groupes phényle non substitués ou substitués ;
 ou dans lesquelles R_1 et R_3 , avec le biradical oxadiméthylène d'interconnexion, forment un hémiacétal substitué par un groupe alkyle en C_1 à C_4 à cycle à 5 à 7 chaînons fermé ;

à condition que R_2 et R_3 ne sont pas des groupes méthyle ;
 A et B sont chacun individuellement des atomes d'hydrogène ou des groupes méthyle, ou bien A et B forment ensemble un groupe méthylène.

2. Composé de vitamine D selon la revendication 1, ayant la formule générale

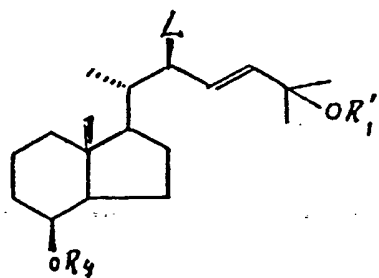


(IV)

dans laquelle :

A et B ont les significations présentées dans la revendication 1, et
R₃' est un groupe alkyle en C₂ à C₆ linéaire ou ramifié, éventuellement substitué par un groupe hydroxy, alcoxy
en C₁ à C₂ ou alkylènedioxy en C₂ à C₃, un groupe cyclopropyle ou un groupe phényle.

3. Composé de vitamine D selon la revendication 2, ayant la formule générale IV présentée dans la revendication 2, dans laquelle les symboles ont les significations présentées dans la revendication 2, étant entendu que C-24, auquel le substituant R₃' est attaché, a la configuration soit R soit S.
4. Procédé de préparation d'un composé de vitamine D selon la revendication 1, caractérisé en ce qu'un composé hydrindane de formule générale

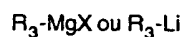


(V)

dans laquelle :

L est un groupe partant, et
R₁' et R₄ sont chacun individuellement des groupes protégeant un groupe hydroxy ;

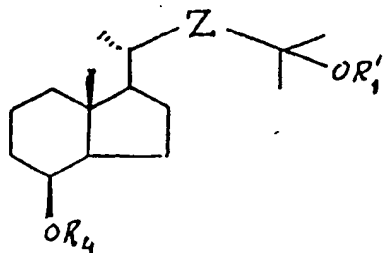
est mis à réagir avec un réactif de formule générale



dans lesquelles :

R₃ a la signification présentée dans la revendication 1, et
X est un atome d'halogène.

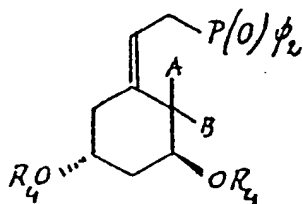
en présence d'un composé de Cu(I) ;
 après quoi le produit intermédiaire hydrindane obtenu, ayant la formule générale



(VI)

dans laquelle Z a la signification présentée dans la revendication 1,
 est oxydé, après déprotection de OR₄, en le composé hydrindane-4-one correspondant, puis est converti, d'une
 manière connue en elle-même pour les composés apparentés,

soit (a) avec un réactif de Wittig de formule générale



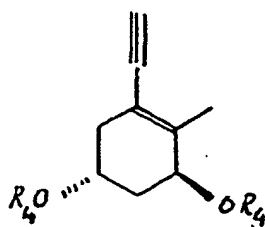
(VII)

dans laquelle :

R₄ a la signification ci-dessus, et

A et B ont les significations présentées dans la revendication 1,

soit (b), après émolisation, avec un composé ényne de formule générale

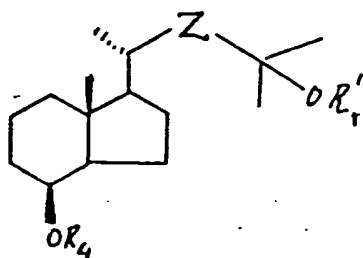


(VIII)

dans laquelle R₄ a aussi la signification ci-dessus, puis est hydrogéné et isomérisé, pour produire un composé
 de formule générale I, dans laquelle A et B forment ensemble un groupe méthylène ;

puis est déprotégé.

5. Produit intermédiaire hydrindane qui peut être utilisé dans le procédé de la revendication 4 et qui a la formule
 générale

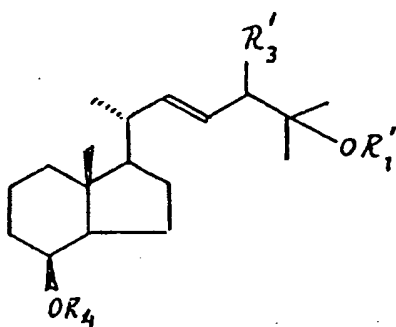


(VI)

dans laquelle :

Z a la signification présentée dans la revendication 1, et
 R_1' et R_4 ont les significations présentées dans la revendication 4.

6. Produit intermédiaire hydriodane selon la revendication 5, ayant la formule générale



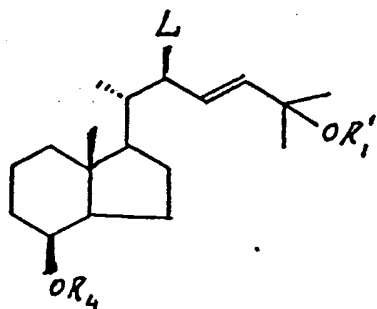
(IX)

dans laquelle :

R_3' a la signification présentée dans la revendication 2, et
 R_1' et R_4 ont les significations présentées dans la revendication 4.

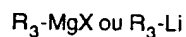
7. Produit intermédiaire hydriodane selon la revendication 6, ayant la formule générale IX, dans laquelle l'atome de C auquel le substituant R_1' est attaché a la configuration soit R soit S.

8. Procédé de préparation d'un produit intermédiaire hydriodane selon la revendication 5, caractérisé en ce qu'un composé de formule générale VI, présentée dans la revendication 5, dans laquelle les symboles ont les significations présentées dans la revendication 5, est préparé en faisant réagir un composé hydriodane de formule générale



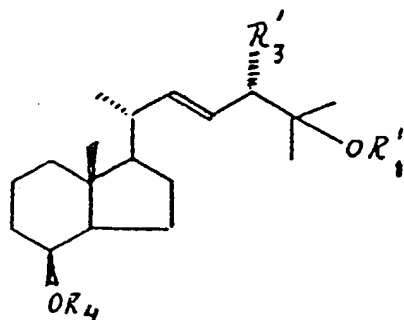
(V)

dans laquelle L, R_1' et R_4 ont les significations présentées dans la revendication 4 ;
 avec un réactif de formule générale



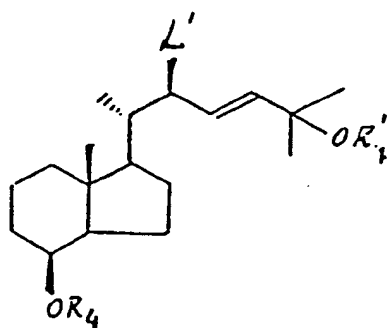
dans lesquelles R_3 a la signification présentée dans la revendication 1, et X est un atome d'halogène, en présence d'un composé de Cu(I).

9. Procédé selon la revendication 8, caractérisé en ce qu'on prépare un composé de formule générale IX, dans laquelle l'atome de C auquel le substituant R_3' est attaché a la configuration de la formule IXA



(IXA)

en faisant réagir un composé hydrindane de formule générale

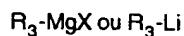


(X)

dans laquelle :

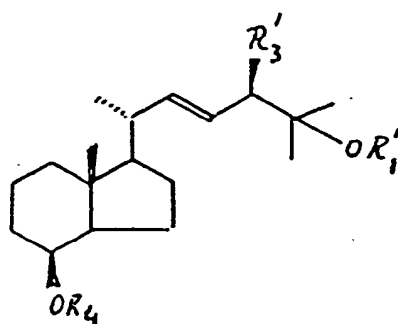
R_1' et R_4 ont les significations présentées dans la revendication 4, et L' est un groupe partant phosphate de di(hydrocarbyle) ;

avec un réactif de formule générale



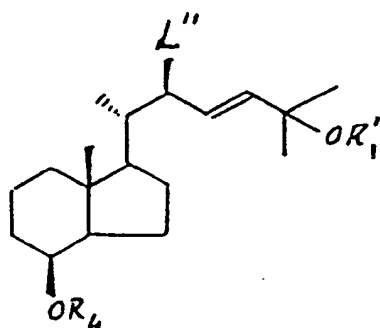
dans lesquelles R_3 a la signification présentée dans la revendication 1, et X est un atome d'halogène, en présence d'un composé de Cu(I).

10. Procédé selon la revendication 8, caractérisé en ce qu'on prépare un composé de formule générale IX, dans laquelle l'atome de C auquel le substituant R_3' est attaché a la configuration de la formule IXB



(IXB)

en faisant réagir un composé hydride de formule générale

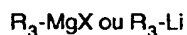


(XI)

dans laquelle :

R_1' et R_4 ont les significations présentées dans la revendication 4, et L'' est un groupe partant carbamate de N-aryle ;

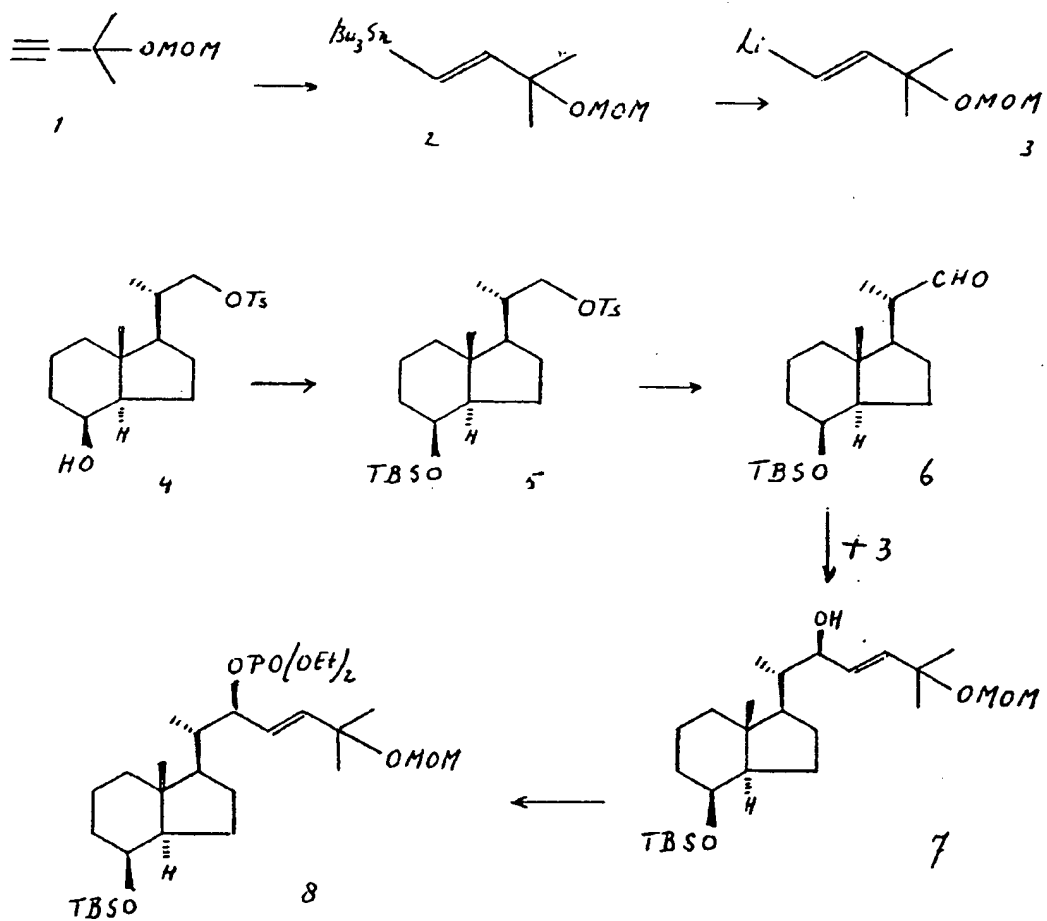
avec un réactif de formule générale



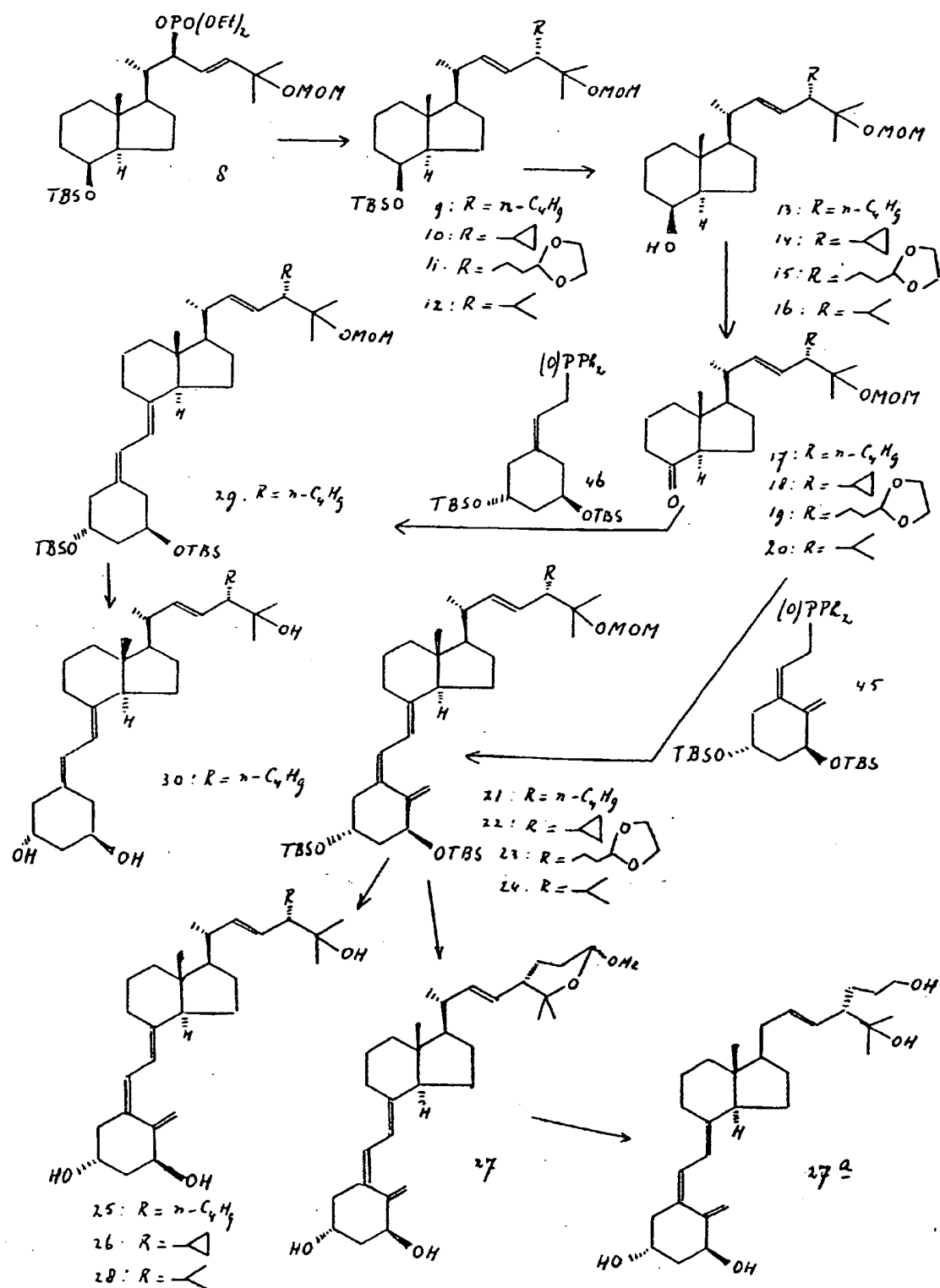
dans lesquelles R_3 a la signification présentée dans la revendication 1, et X est un atome d'halogène, en présence d'un composé de Cu(I).

11. Composition pharmaceutique, comprenant, en plus d'un véhicule pharmaceutiquement acceptable et/ou d'au moins une substance auxiliaire pharmaceutiquement acceptable, en tant que principe actif, au moins un composé tel que défini dans la revendication 1, 2 ou 3, en une quantité efficace.

12. Composition selon la revendication 11, lorsqu'elle est utilisée dans un procédé pour le traitement et/ou la prévention d'un certain nombre de maladies de la peau ou d'un certain nombre de maladies, incluant des maladies osseuses telles que l'ostéoporose, l'ostéodystrophie rénale et l'ostéomalacie, des maladies auto-immunes, l'acné, l'alopécie, le vieillissement de la peau, un déséquilibre du système immunitaire, des maladies inflammatoires telles que la polyarthrite rhumatoïde et l'asthme, ainsi que des maladies liées à une différenciation et/ou prolifération cellulaires anormales, ainsi que des cancers solides, de la peau ou du sang, chez un être vivant à sang chaud, comprenant l'administration audit être ou le traitement dudit être avec une composition selon la revendication 11 en une quantité efficace pour l'objectif recherché.

Reaction Scheme A

Reaction Scheme B



Reaction Scheme C

